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REACTIONS TO THE PARENTERAL INTRODUCTION OF HORSE SERUM IN MAN

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The parenteral introduction of foreign protein in the form of antiserums is accompanied in a large proportion of cases by local and constitutional manifestations of irritation or intoxication. Such manifestations consist, in the majority of cases, in the development of urticarial and erythematous eruptions, joint or muscle pains, pyrexia and occasionally vomiting.

Such manifestations of the disease, though they may be annoying to the affected individual, and although, occasionally, the onset of an unexplained pyrexia in the course of the treatment of the wounded may cause anxiety to the surgeon in charge, are of comparatively little importance.

Unfortunately there occasionally occur, within a short time after the injection of the serum, more serious reactions. The symptoms in these cases comprise collapse, tachycardia, drop in blood pressure, unconsciousness, and occasionally difficulty or arrest of respiration with consequent cyanosis and air hunger. Such cases are often fatal.

In consequence of the very large number of serum injections performed during the war both in normal and previously injected persons, there has been a unique opportunity of studying the reaction of the human tissues to the parenteral introduction of horse serum protein. It is upon the results of observations upon soldiers, both in France and Canada, that this contribution is based.

Before proceeding to an analysis of the cases reported in this paper, it is proper to review the symptoms and signs of anaphylaxis as noted in experimental animals.

In the dog, the predominant reaction is one in which drop in blood pressure and acceleration of the heart rate are the most striking clinical features. Vomiting and diarrhea, the latter frequently bloody, are common. At necropsy, extreme dilatation of the vessels draining the upper abdominal viscera is noted. The liver, spleen, and kidney are congested, and the veins of the upper intestinal tract are distended. The bowel wall, in rapidly fatal reactions, is deep purple in color.

If the injections are made subcutaneously the reaction is not usually fatal, but is similar in nature. In the event of either a subcutaneous or intravenous injection having produced severe shock, which does not immediately prove fatal, there often supervenes a period during which the animal appears to have returned to normal. In some cases following such a period, there is a second onset of symptoms after the lapse of from two to twelve hours. This delayed reaction is similar in nature to the first, is more protracted, and is often fatal.

As compared with the splanchnic dilatation and consequent drop in blood pressure in the dog, the guinea-pig presents a very different picture, although this animal, too, is readily "shocked" by the parenteral introduction of the protein to which it has been sensitized. If the sensitized guinea-pig is injected intravenously with a small dose of protein, there is an almost immediate onset of symptoms. These symptoms consist of itchiness of the skin, as evidenced by the animal's scratching itself, excitability, convulsive seizures and paralysis, usually noted in the loss of power in the hind legs. The animal suffers from difficulty in breathing. Cyanosis develops and the animal dies from an arrest of respiration.

If immediate necropsy is performed, the heart will be found still beating. The lungs are voluminous, with rounded borders, and exhibit small hemorrhagic foci over the surface.

Occasionally, in guinea-pigs, more particularly in those that die at the end of from six to ten minutes following intravenous injection, there is evidence at necropsy of marked splanchnic dilatation.

If the guinea-pig receives its dose of serum subcutaneously or intraperitoneally, the onset of the reaction is delayed, is less severe, the amount of protein injected being the same and is frequently accompanied by a rigor as evidenced by the animal's shivering. A definitely delayed reaction following upon a period of apparent return to normal takes place less frequently in the guinea-pig than in the dog, but does sometimes occur.

In the rabbit, urticaria and localized cellulitis, accompanied occasionally by necrosis, about the site of subcutaneous injections, takes place in sensitized animals; and it is in these animals that such manifestations have been more generally studied (Arthus' phenomenon). The rabbit may also be so sensitized and shocked that dyspnea, convulsions, diarrhea and sometimes death may result.

In addition to the clinical manifestations noted herewith, examination of the blood of shocked animals may reveal diminution in complement content, leukopenia or leukocytosis and lengthening of coagulation time, as well as blood concentration.

It is evident from this brief résumé that different species of animals react in a manner typical for that species. Such a typical reaction occurs irrespective of the source of the protein. It is also evident that no one symptom is characteristic of the anaphylactic reaction in all animals, although in all animals the involuntary muscle tissue is apparently chiefly affected by the irritant.[1] The manifestations of intoxication are, moreover, influenced in the same animal by the size of the dose of protein, and the route of administration, as well as by the degree of hypersensitiveness on the part of the animal.

In man, it is evident from a study of cases that reactions of all three types occur, namely, urticaria and cellulitis, splanchnic dilatation and respiratory anaphylaxis, as in the guinea-pig. It would appear that both as a primary cause of death and also as subjecting the patient to the danger of a delayed reaction the splanchnic type is of most importance.

The cases which are analyzed in the following pages have been grouped under three headings:

1. Severe immediate general reactions: (*a*) death; (*b*) recovery.
2. Immediate focal reactions and moderately severe early reactions.
3. Focal and general delayed reactions.

I. SEVERE IMMEDIATE GENERAL REACTIONS—ANAPHYLACTIC SHOCK

Two cases that terminated fatally I have observed personally, and the notes of one case, hitherto unpublished, have been placed at my disposal. In addition to an analysis of these cases, three cases which have been recently reported in the English and American literature are employed.

In three of these six cases, death supervened following intravenous injection of the serum protein. In the remaining three, the route of administration was subcutaneous (possibly intramuscular).

Four cases are reviewed in which severe immediate reactions occurred, which, however, were not followed by a fatal termination. Reports of two of these cases are published for the first time, two have recently been reported in the literature (Tables 1 and 2).

In those cases in which the splanchnic type of reaction predominated, there occurred collapse, pallor, tachycardia, thready pulse, pain in the epigastrium and over the heart, increased intestinal peristalsis, rectal tenesmus, vomiting and blood concentration. The recurrent type of reaction occurred in half of the fatal cases.

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1. Simonds, J. P.: The Fundamental Physiologic Reaction in Anaphylactic and Peptone Shock, J. A. M. A. **73**:1437 (Nov. 8) 1919.

The respiratory type of reaction was characterized by choking sensations, cyanosis, asthmatic dyspnea and arrest of respiration.

The cutaneous phenomena consisted of erythema urticaria and "angioneurotic" edema.

It is evident from Tables 1 and 2 and from the subjoined case reports that in many cases both splanchnic and respiratory reactions took place, and in three of the four nonfatal cases, cutaneous phenomena were noted.

An abstract of a case report [2] of a healthy man who collapsed following the hypodermic administration of a relatively small dose, 5 c.c. of horse serum, and who died with symptoms during life identical with those which occur in anaphylactic shock in the dog, is given herewith. Necropsy findings were identical with those which are found in the guinea-pig.

REPORT OF CASES

CASE 1.—Sgt. E., aged 30, was given 5 c.c. of serum subcutaneously over the right pectoralis major at 11:15 a. m., Sept. 1, 1916. He was in good general condition, the wounds from which he was suffering being trivial.

At 1:30 p. m., he commenced to vomit and a bloody diarrhea developed. This gastro-intestinal disturbance was accompanied by a moderate degree of collapse. At 5 p. m., his pulse was 104 and his temperature 102.8 F. He complained of moderate headache and thirst; there was slight generalized abdominal tenderness, but no rigidity. He made no complaint of respiratory distress, despite the fact that he was cyanosed and restless. The skin was "goose-fleshed" and covered with a mild erythema.

Until 11 p. m. his condition remained somewhat relieved. No treatment was instituted as his condition was not considered alarming.

At 11 p. m., after a slight vomiting attack, the collapse became very severe. He became pulseless at the radials; the heart beat rose to from 160 to 170 per minute. He became extremely cyanosed, and restlessness increased. During the night, stimulation was pressed to the utmost. Pituitary extract, 1 c.c. to the dose, was given every three hours. One-thirtieth grain of strychnin was given at 11 p. m., and its administration was continued in doses of one-fortieth grain every three hours. He received three pints of saline subcutaneously during the night, and oxygen was given almost continuously up to the time of death. Except for the fact that he became quieter and more comfortable while receiving oxygen, there was no response to stimulation.

At 6 a. m., September 2, these notes were made: "Pulse is absent at the wrist, heart rate 180 and feeble. There is a very marked purplish discoloration (cyanotic erythema) of the whole body. This discoloration disappears on pressure and returns very slowly. The extremities are cold. There has been no return of vomiting or diarrhea."

Death ensued at 10:30 a. m., apparently due to cardiac failure secondary to drop in blood pressure. Respirations during the last three hours of life were at the rate of from 48 to 54 per minute.

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2. Gurd, F. B., and Emrys-Roberts, E.: Fatal Anaphylaxis, Lancet 1:763 (April 3) 1920.

TABLE 1.—Reactions Following the Administration of Serum Protein in Six Fatal Cases

Case	Author	Route of Administration	Amount Injected in C.c.	Dilution	Length of Time Supervening Before Onset of Symptoms	Length of Time Between Injection and Death	Type of Action	Treatment Employed	Most Striking Features
1	Gurd	Subcutaneous	5	Undiluted	135 Min.	19 Hrs.	Splanchnic recurrent (respiratory)	Pituitary extract, strychnin, subcutaneous saline	Collapse, cyanosis, erythema, recurrent collapse
2	Gurd	Subcutaneous	5	Undiluted	150 Min.	11 Hrs.	Splanchnic recurrent	Intravenous glucose saline, epinephrin	Collapse, response to epinephrin
3	Gurd	Intravenous	2	Undiluted	Immediate	10-15 Min.	Respiratory	Artificial respiration	Strong slow pulse; absence of splanchnic reaction
4	Boughton	Intravenous	1/10	Undiluted	2 Min.	45 Min.	Respiratory (splanchnic)	Epinephrin	Asthmatic attack; response to epinephrin
5	McCallum	Subcutaneous	5	Undiluted	2 Min.	5 Min.	Splanchnic primary	None	Epigastric discomfort; rectal tenesmus
7	Patrick	Intravenous	5	1/50	3 Min.	36 Hrs.	Splanchnic recurrent	None	Loss of consciousness; rapid appearance of urticaria

TABLE 2.—Severe Immediate Reactions Followed by Recovery

Case	Author	Route of Administration	Amount Injected in C.c.	Dilution	Length of Time Supervening Before Onset of Symptoms	Duration of Symptoms	Type of Action	Treatment Employed	Most Striking Features
9	Gurd	Intradermic	0.25	Undiluted	15 Min.	4-6 Hrs.	Respiratory urticaria	None	Extreme edema of face and at site of injection
10	Gurd	Subcutaneous	5	Undiluted	2-4 Hrs.	12 Hrs.	Splanchnic urticaria	Calcium lactate	Vomiting; blood concentration
11	Munro	Intravenous	30	Diluted	1 Min.	5 Min.	Respiratory (splanchnic)	Posture, artificial respiration, epinephrin, atropin, chloroform	Recovery of most desperate case; use of chloroform
6	Patrick	Intravenous	20	1/50	1½ Min.	Few minutes	Splanchnic urticaria 24 hrs.	None	Pain over heart

Necropsy was performed four hours after death. Owing to the presence of pleural adhesions, the lungs were squeezed considerably in the process of removal, nevertheless, they were voluminous and downy, except over the posterior parts which were boggy and dark in color. The lungs were reddish gray and were covered over the whole surface with innumerable subpleural collections of deep purple blood. These patches [3] varied in size from 1.5 to 5 mm.

Beneath the parietal pleura there was a smaller number of similar hemorrhagic spots.

The cut surface of the posterior parts exuded a considerable amount of bloody frothy fluid; the anterior portions showed a dilatation of the alveoli and numerous small purplish red spots.

The upper intestinal tract showed slight capillary dilatation.

So far as we are able to discover, the patient had not been previously wounded nor had he received at any other time injections of horse serum. That he was an individual presenting a natural hypersensitiveness to horse serum is therefore a fair assumption. The fact that the same person is not infrequently sensitive to more than one foreign protein in all probability offers an explanation of the patient's history of repeated attacks of vomiting and bloody diarrhea.

Inasmuch as the patient in Case 2 was not under observation by any one medical officer during the period intervening between the time of serum injection and his death, there is perhaps some slight doubt regarding the nature of the collapse that resulted. Correspondence was, however, carried on with those officers who had seen the patient prior to admission to the casualty clearing station, and the note made by the officer in charge of the patient at the main station of the field ambulance stated that "while in the field ambulance, he appeared to be suffering slightly from shock, but in other respects was in good condition when he left the main dressing station."

Case 2.—S. M. was admitted to the casualty clearing station six hours after being wounded and three hours after receiving serum injection at the field ambulance.

His injury consisted of a perforating wound of the upper third of the left thigh behind the bone. No large vessel was injured; there was no evidence of hemorrhage; the sciatic nerve was intact and there was no important laceration of muscle. Briefly, the wound was of such a nature as was considered trivial, infection excluded.

He was admitted at 8:30 a. m. On admission his condition was seen to be extremely grave; he was pale, slaty in color and mentally stuporous. The mucous membranes were not blanched. The pulse was barely perceptible at the radials; the rate was over 140 per minute. There was no respiratory difficulty, no urticaria and the extremities were cold.

The patient was placed under an incandescent heater with the foot of the bed raised; but no improvement occurred. On the contrary he appeared to

3. These hemorrhagic patches are typical of those found in anaphylaxis in the guinea-pig.

become worse. An operation was therefore performed at 2 p. m., as it was feared that despite negative findings he might be suffering from a deep seated gas gangrene.

Examination of the wound was made under gas and oxygen anesthesia. An intravenous saline solution containing 7.5 per cent. glucose, to which was added 8 mm. of epinephrin, was given. Fifteen hundred c.c. was thus injected. During the induction of anesthesia (nitrous oxid and oxygen) collapse of the patient became almost complete. Respiration ceased and the heart sounds became almost inaudible. The rate of flow of the intravenous solution was increased, and artificial respiration was employed. This resulted in return of signs of life. After 500 c.c. of the solution had been injected, there was marked improvement in the patient's condition, and at the time of the completion of the injection of the total quantity of 1,500 c.c. the patient's pulse rate was 86, of good pressure, and his color was good. Evidently he had lost no important amount of blood. He became mentally alert and remarked that he had felt "all in," but that he was now fit. The operation itself consisted simply in an incision of the affected part for purposes of examination. Carrel tubes were inserted. The whole procedure occupied but three or four minutes. Examination revealed no evidence whatever of gas gangrene.

He returned to the ward in good condition, "practically normal in appearance," and remained fit for approximately thirty minutes, when he rapidly collapsed, and died at 4:30 p. m. Unfortunately, owing to pressure of work in the operating room, it was not possible to see him during this second period of collapse.

Necropsy was performed thirty minutes after death. There were no positive findings other than enlargement of all the great and smaller veins in the splanchnic area. After removal of the heart, the right thorax filled immediately with fluid blood up to two thirds of its capacity. Examination of the leg confirmed the absence of gas gangrene.

There is no doubt in my opinion that this was a case of fatal anaphylaxis following the subcutaneous administration of a small dose (presumably about 5 c.c.) of antitetanus serum. This belief is based upon the absence of any other cause of shock or infection, and upon the very prompt response to the glucose injection with its epinephrin content. At necropsy, as mentioned above, the only abnormality was the extreme content of blood in the veins and capillaries of the splanchnic area and the absence of clotting one-half hour after death. One cannot help feeling it was unfortunate that circumstances were such that we were unable to repeat the epinephrin injection at the time of his second collapse.

For notes regarding the following case I am indebted to Dr. Edward W. Archibald of Montreal.

Case 3.—The patient received a gunshot wound of both legs in October, 1915. Severe infection of all wounds occurred; drainage was instituted, but his condition remained unsatisfactory, and two weeks after admission to the hospital a blood culture proved that he had a streptococcus septicemia. There is some doubt as to whether he had received tetanus serum at the field ambu-

lance. Although no note of such was made on his card, it is probable that such an injection had been made.

Upon discovery of the blood infection, he was given a dose of antistreptococcic serum. This was injected undiluted intravenously. The material was injected very slowly. After he had received 2 c.c., symptoms of anaphylaxis supervened. He complained of feeling queer and tight across the chest. Respirations increased somewhat in rate and became more labored. The pulse remained strong and comparatively slow until he died. Death occurred between ten and fifteen minutes after the onset of symptoms.

Dr. Archibald's notes state that the chief trouble seemed to be with his respiration. His face took on an anxious expression, and he became pale. He was quite conscious for several minutes and then became unconscious. Involuntary micturition and defecation occurred. Artificial respiration was employed but without avail.

At necropsy the lungs were found to be voluminous with subpleural ecchymoses.

Boughton [4] reports a case (Case 4) of anaphylactic death occurring in an asthmatic following an intravenous injection of 1 minim of normal horse serum undiluted.

CASE 4.—"Within two minutes a typical attack of asthma supervened. He was given 10 minims of epinephrin intravenously with definite relief for about ten minutes." Four other similar doses were given, each gave relief for several minutes, but the patient died forty-five minutes after the injection of serum.

Necropsy was performed within half an hour after death. The face was cyanotic and the lips swollen. "The abdominal cavity showed intense injection of the vessels everywhere, being especially marked in the veins of the stomach, mesentery, gallbladder and appendix. The entire small intestine was bright red and the dilated submucous vessels showed distinctly through the intestinal wall. The parietal peritoneum was markedly injected; no exudate was visible in the peritoneal cavity.

"Both lungs were enormously distended and emphysematous. The left lung showed small areas of hemorrhage at the lateral portion of the lower lobe, about 4 cm. in diameter, with a gelatinous organizing exudate at this point. On section the lungs were found to be dry. Microscopically the lungs showed passive hyperemia but no edema; there were a few small interstitial hemorrhages." Microscopic examination of the kidneys revealed the most marked changes: "The epithelium of the convoluted tubules was distinctly edematous and there was considerable degeneration and some necrosis; there was intense passive hyperemia. Interstitial hemorrhages were numerous but not extensive."

McCallum [5] reports a case (Case 5) of fatal anaphylaxis following the prophylactic injection of diphtheria antitoxin subcutaneously.

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4. Boughton, T. H.: Anaphylactic Death in Asthmatics, J. A. M. A. **73**:1912 (Dec. 27) 1919.

5. McCallum, D.: Fatal Anaphylaxis Following Prophylactic Injection of Diphtheria Antitoxin Subcutaneously, Brit. M. J. **2**:596 (Nov. 8) 1919.

Case 5.—The patient was a boy, aged 8, apparently healthy. Following the injection of 2,000 units (amount of serum not stated), death occurred in five minutes. Two minutes after the injection was made, the boy made the complaint that "it had gone to his stomach." He ran out of the house to the privy in the backyard. One minute later, he was heard calling, "Daddy, Daddy." His father immediately ran to his assistance and found him completely collapsed and apparently choking. His whole body was deeply cyanosed; he was pulseless. Artificial respiration was employed without avail.

Necropsy was performed. No note regarding the condition of the lungs nor splanchnic region is published.

Patrick [6] reports three cases of anaphylaxis occurring in patients who received intravenous injections of horse serum in the treatment of bacillary dysentery.

Case 6.—His first patient was not known to have received serum injections previously. During seven days, he received 85 c.c. in five divided doses of about 20 c.c. each.

"About one and one-half minutes after the last injection, the patient experienced sudden pain over the heart, became pale and felt faint. He felt all right again within a few minutes. A serum rash covered the body by the following day. His convalescence was rapid."

Case 7 (Patrick's Case 2).—Antidysenteric serum was administered subcutaneously twenty-six days before the intravenous dose, which was accompanied by anaphylactic shock.

Twenty-five c.c. of serum were diluted in saline up to 1,000 c.c. Three minutes after the commencement of the injection of serum, the patient complained of pain across the chest. He became restless, stretched out his arms. His eyes became wide and staring. He probably lost consciousness for a few seconds; the heart sounds remained steady and there was no sign of cardiac dilatation. Injection was stopped.

Five minutes later his condition appeared normal and the injection of saline containing serum was resumed. Seven minutes after the resumption of the injection an urticarial rash began to appear on the arm, apparently along the line of the vein into which the fluid was being injected. Within a few minutes urticarial patches had appeared on the forearm, hands, and upper part of the trunk. They were not observed elsewhere. The total quantity of serum and saline was injected in twenty minutes. Five minutes after the completion of the injection, all traces of urticaria had disappeared.

The injection was completed at midnight. During the night, the patient vomited a great deal, and died the following day, though immediately following the injection his condition appeared improved.

At necropsy, in addition to the dysenteric findings, the stomach was found to be much distended, and there was great dilatation of the duodenum which had a diameter equal to that of a normal stomach.

Case 8.—The third patient (Case 6) had received antitetanus serum, after being wounded sometime before. In the treatment for dysentery, 50 c.c. of antidysenteric serum were diluted in 1,000 c.c. of saline, and intravenous injection was commenced. When not more than 50 c.c. of the mixed fluid had been run

6. Patrick, C. A.: Anaphylactic Shock After Injection of Serum Intravenously, Brit. M. J. **2**:114 (July 28) 1917.

into the vein, he suddenly became very ill, his eyes became staring, and his arms stretched out. His face was pale and he had become unconscious. Breathing stopped for about thirty seconds. Within a few minutes he looked quieter, but remained unconscious for about two hours with a rapid pulse. In the evening (injection had taken place at 2 p. m.) he improved and was able to answer questions. No rash was seen. He had a restless night but was slightly better in the morning. He died the following morning.

Necropsy notes refer simply to the dysenteric condition.

Patrick refers to the severe pain in the chest as being one of the most striking phenomena, but draws attention to the fact that overfilling of the heart could not have been held responsible, as the injection was being carried on very slowly and was small in amount.

Case 9.—Lieut. H. was admitted to the casualty clearing station on account of asthma, which the patient himself believed to follow proximity to horses. An effort was made to confirm his sensitiveness to horse protein, and to determine the degree of sensitiveness to horse serum. At 11:30 a. m., Nov. 12, 1915, 0.25 c.c. of horse serum was injected intradermically into the skin on the outer border of the left upper arm. Fifteen minutes later there was an onset of coryza and an asthmatic attack occurred which increased for about twenty minutes. At its maximum, it was slightly to moderately severe. A marked swelling of the face and ears, more particularly of the eyelids, occurred to such a degree that he was unable to see. The lobes of both ears filled with fluid and hung well down on his neck. At the site of injection there was an edematous enlargement, about the size and shape of a hen's egg, which hung down, having the appearance of a supernumerary breast. This reaction persisted, though gradually subsiding, for from four to six hours.

The effect of this reaction to the injection was more marked than was anticipated and suggests that the dose used (0.25 c.c.) was unnecessarily large for the purpose of confirmation or diagnosis.

The following day, November 13, at 11 a. m., he was injected with 0.15 c.c. of horse serum subcutaneously; no reaction occurred. At 12:30 the same day he received 0.25 c.c. intramuscularly; no reaction either local or general took place. At 2 p. m. of the same day, he received 0.5 c.c. subcutaneously, again without reaction.

The patient was unwilling to remain in the hospital longer, and seemed satisfied to have the cause of the asthma definitely established, hence it was impossible to attempt immunization. The experiment does prove a very great hypersensitiveness to horse protein in a patient who thought himself to be subject to asthma when in the presence of horses, and also the possibility of desensitizing by means of a dose of 0.25 c.c. of horse serum.

The patient was discharged from the hospital with a note given to him to the effect that prophylactic or therapeutic injections of horse serum should not be employed unless such was preceded by a desensitizing dose.

For the following notes I am indebted to Major John Fraser, M. C.

Case 10.—The patient was wounded June 29, 1917. His injury consisted of a small perforating wound of the right upper arm. Five hundred units of antitetanus serum were administered at the field ambulance. Upon admission

to the casualty clearing station, three or four hours later, the patient was pulseless, his body was covered by a hyperemic rash, there was a generalized edema of the whole body and he was vomiting frequently. Blood count demonstrated: hemoglobin, 110 per cent.; erythrocytes, 8,240,000, and leukocytes, 25,000.

Calcium lactate was given in doses of 15 grains, three times a day. Improvement in the patient's general condition followed after the third dose.

The following day the patient's condition was satisfactory. Blood count showed: hemoglobin, 82 per cent.; erythrocytes, 6,100,000, and leukocytes, 13,000.

An important case of severe anaphylaxis following the administration of horse serum with recovery, is reported by Munro.[7] This case is of interest on account of the description of symptoms, and also on account of the satisfactory result which followed the treatment as instituted by Munro.

CASE 11.—The patient, who had received prophylactic antitetanus serum subcutaneously when wounded, came under Munro's care suffering from erysipelas of the leg. In the treatment of the latter, he was given 30 c.c. of antistreptococcic serum intravenously. The serum was diluted. The extent of dilution is not stated in the article. No effort was made to desensitize the patient. Within one minute after the injection, the patient complained of choking, he grasped his larynx, breathed jerkily and spasmodically. Extreme cyanosis developed and the pulse became flickering. Breathing ceased in full inspiration. Treatment was instituted at once; the head of the bed was lowered and artificial respiration was commenced. Epinephrin, 30 minims, and atropin, 1/100 grain, were given subcutaneously, and chloroform was placed on a mask through which all air which entered the lungs during artificial respiration had to pass.

Within five minutes, the patient's condition improved; normal breathing commenced; the pulse returned at the wrist, and was counted at 150 per minute. The patient later made an excellent recovery.

In this case, the reaction was almost exclusively respiratory in nature, and in this respect should be compared with Case 5 in which the manifestations of splanchnic dilatation predominated.

II. IMMEDIATE FOCAL REACTIONS

If the hypersensitive individual receives an injection of serum into tissues in which the injected protein is exposed to the action of only a small portion of the body fluid or blood stream, the protein is but slowly acted upon by the anaphylactic bodies. In consequence, instead of a fulminant systemic reaction taking place, there may occur simply a focal reaction to the presence in the tissues of an irritant foreign substance. In other words, inflammation develops at the site of injection.

The following case is an example of the cellulitis type of local allergic reaction which occurs in cases of serum hypersensitiveness.

7. Munro, W. T.: A Case of Anaphylaxis, Brit. M. J. **2**:668 (Nov. 22) 1919.

TABLE 3.—Summary of Cases Illustrating Immediate and Delayed Focal and General Reactions to Serum Protein

Case	Route of Administration	Amount Inoculated, C.c.	Time Since Last Injection	Time Between Injection and Reaction	Type of Reaction	Duration of Reaction	Most Striking Feature
12	Subcutaneous	4	21 days	4 hours	Local cellulitis (severe); pyrexia 103 F.	4 days	Typical cellulitis of thigh
13	Subcutaneous	3.5	25 days	2 hours	Local cellulitis (severe); headache; joint pains; pyrexia 102 F.	3 days	Typical cellulitis of arm
14	Subcutaneous	4	10 months	Immediate	Local cellulitis; generalized itchy urticaria	7 hours	Apparent response of urticaria to calcium chlorid
15	Intradermic	1	2 months	30 minutes	Local cellulitis	Short duration	Desensitization as evidenced by injection of 5 c.c. 3 hours after primary injection without reaction
16	Subcutaneous	10	.....	2 days	Local cellulitis; pyrexia 105 F.; headache	24 hours	High fever, 105 F.
17a	Intradermic	1	6 weeks	Immediate	Mild hyperemia	Short duration	Dose sufficed to desensitize
17b	Intramuscular, thigh	75	2 hours	3 days, 5 days	Marked edema, locally; moderate urticaria	5 days	Extensive edema in injected tissues
17c	Intradermic, forearm	0.25	20 days	Immediate	Local cellulitis; lymphangitis; lymphadenitis	12-24 hours	Focal reaction at site of injection of serum twenty days previously
				4 hours	Focal reaction; thigh	3-24 hours	
18	Intradermic	0.5	15 days, 500 C.c.	.....	No reaction	.....	Absence of reaction due to immunity or tolerance
19a	Subcutaneous	10	18 months (6 doses)	4 days	Pyrexia 104 F.; local urticaria and moderate cellulitis	2 days	Malaise
19b	Intradermic	0.25	24 days	2½ minutes	Local cellulitis; lymphangitis	80 minutes	Prompt local reaction of short duration
					Purulent reaction	1 week	Pus cell accumulation
19c	Subcutaneous	2	2 hours	1 hour or less	Deep cellulitis; pyrexia 100.4 F.	2 days	0.25 c.c. of serum failed to desensitize; reaction at site of injection 24 days previously
20	Subcutaneous	5	7 days	24 hours	Pyrexia 100.4 F.; malaise; cellulitis	9 days	Large abscess formation
				4 days	Local abscess formation		
21 Treadgold	Subcutaneous	10	No previous injection	6 days	Local urticaria; joint pains; malaise; pyrexia 100 F.	7 days from commencement of reaction to return to normal	Gradual increase in severity of symptoms of intoxication; edema of glottis
				7 days	Lymphadenitis (local)		
				8 days	Generalized giant urticaria; generalized lymphadenitis; pyrexia 103.4 F.		
				9 days	Weak rapid heart action; buccal urticaria; edema of glottis		
22 (Type)	Subcutaneous	10	.....	8 days	Local urticaria with tenderness; pyrexia 100-101 F.; generalized urticaria; anorexia and malaise	2-4 days	No symptoms causing anxiety or very annoying to patient; type of reaction usually occurring in previously uninjured individuals

In this case the reaction was well established at the end of four hours and persisted for four days, accompanied by fever.

CASE 12.—Pte. A. M. D., while working on the barbed wire in "No Man's Land," three weeks prior to admission, suffered a small tear below the right knee. At that time he received a routine dose of antitetanus serum. He was admitted to the casualty clearing station on account of a slight infection of the tissues about the abrasion. The temperature was 100 F. and the pulse 88.

On admission, a small incision was made into the infected area, and 750 units of antitetanus serum, contained in 4 c.c. of serum, were administered into the right thigh at 5 p. m. Four hours later, at 9 p. m., the patient complained of pain in the thigh. His temperature was 103 F., his pulse 116. The following morning the temperature was 103 and the pulse 116. The anterior surface of the thigh about the point of serum injection was swollen, hot, red, painful, tender and edematous. Immediately about the point of the needle puncture, there was some itchiness. The wound below the knee was dressed and found to be free from pus. During the next twenty-four hours, the cellulitis of the thigh became more marked. It then commenced to subside, without further treatment. On the fifth day after the injection, the thigh showed but slight induration, and the temperature was normal.

In view of the fact that the cellulitis subsided, although no treatment whatever was instituted, and in view of the prompt onset of the reaction at the site of serum injection, it would appear that the inflammation was a local allergic reaction consequent upon the injection of horse serum into the tissues of an individual who had been sensitized by a dose given three weeks previously.

A similar instance is Case 13.

CASE 13.—Pte. A. G. H. suffered a bullet wound of the hand Feb. 19, 1918, on which date he received 750 units of antitetanus serum. The following day he had a generalized urticaria. Between three and four weeks later, on March 23, he was given a dose of 500 units subcutaneously in the left arm. Two hours later, the arm became swollen, red, and very painful, and he complained of headache and joint pains all over the body. His temperature, which had previously been normal, rose to 102 F. The following day there developed a severe cellulitis of the left upper arm. This was judged to be a serum reaction; no treatment was employed. During the next three days, the hyperemia and swelling subsided entirely.

In Case 14, in addition to an immediate focal reaction at the site of reinjection (ten months after sensitizing doses), a generalized urticaria developed within six hours. The latter subsided promptly following the administration of calcium chlorid.

CASE 14.—Sgt. E. W. was wounded Oct. 1, 1916. Serum was given on the same day, and was repeated on the fifth day. It is presumed that on each of these occasions he received approximately 5 c.c.

He was again wounded Aug. 15, 1917. At 3 a. m. of the same day, he received 750 units of antitetanus serum. He states that an immediate painful

and tender local reaction occurred. When first seen at the casualty clearing station at 9 a. m., he was suffering from a generalized marked itchy urticaria. He received at once 1 dram of calcium chlorid in four divided doses, at fifteen minute intervals. The urticaria subsided promptly.

The following represents a typical case of immediate focal reaction to the intradermic injection of 1 c.c. of serum, two months after a previous dose. This case is also of interest since it demonstrates that 1 c.c. of serum desensitized the patient completely.

Case 15.—Pte. G. M. was wounded Sept. 6, 1916, at which time he received a routine dose of antitetanus serum. He returned to duty and was again wounded Nov. 6, 1916. His wound consisted of an entrance and exit wound of the left thigh. In view of the fact that he had recently received an injection of horse serum, no antitetanus serum was administered at the field ambulance.

On November 7, at 11 a. m., an injection of 1 c.c. of serum was administered intradermically into the upper right arm. Thirty minutes later, there was a hyperemic swelling with a clean-cut edge measuring 6.5 cm. in diameter. The surrounding area was slightly itchy.

At 2 p. m. of the same day (Nov. 7), he received 5 c.c. of serum, representing 750 units, subcutaneously in the pectoral region. No reaction other than slight soreness at the site of injection supervened.

In Case 16, the reaction occurred on the second day following the serum injection. Focal cellulitis accompanied by a febrile reaction took place. The temperature rose to 105 F.

Case 16.—Pte. H. K. P. sustained an unimportant wound of the left buttock, March 31, 1917. On the same day, he was given 1,500 units of antitetanus serum. April 2, the left side of the chest, at the site of serum injection, became swollen and reddened, slightly tender, but not itchy. His temperature rose to 105, the pulse to 116, and remained high for twenty-four hours. Except for headache, which accompanied the fever, and the swelling of the side of the chest, there were no other symptoms.

Case 17 is of interest since it appears to prove that serum, injected into the muscles of the body, remains in situ, more or less unaltered, for at least three weeks.

Case 17.—P. J. was wounded Nov. 5, 1916, on which date he received a routine dose of 750 (U.S.A.) units of antitetanus serum at the field ambulance. His wound consisted of comminuted fractures involving the left knee joint. December 22, an attack of tetanus developed. He had received no subsequent doses of antitetanus serum during the interval.

Before commencing the treatment of the tetanus, the patient was given intradermically a desensitizing dose of 1 c.c. of serum. Slight hyperemia immediately developed about the injection area, otherwise no reaction occurred (Table 3, Case 17*a*). During the next three days he received 13,500 units of serum into the muscles on the anterior part of the thigh, in order, if possible, to bathe the filaments of the anterior crural nerve, which was thought to be the nerve involved in transmitting the toxin upward. This antitetanus content

required about 75 c.c. of serum. The course of the tetanus infection was benign, all symptoms having disappeared by Jan. 2, 1917.

During the night following the third day's injection into the thigh, the left thigh and foot commenced to swell; this swelling increased in size for forty-eight hours, until the thigh became almost twice the size of its fellow (Table 3, Case 17*b*). The leg and thigh were very edematous, slightly painful, and moderately tender. The swelling pitted upon pressure, impressions from 2 to 3 cm. in depth being easily produced.

On the fifth day, following the beginning of the injections, the whole body was covered by a mild to moderate grade of itchy urticaria. No joint or other pains, besides those in the left leg and thigh, occurred. The swelling of the leg, though gradually subsiding, persisted for several days, and returned to normal five or six days after its commencement.

This local delayed allergic reaction is of great interest, not only since it demonstrates in a very striking manner the development of a typical allergic reaction several days (five) after the introduction of the protein, but also since it indicates that although, as other experiments prove, the antitoxin content of the serum is easily available for use in the tissues following intramuscular injection, part at least of the protein serum remains in situ for at least five days.

Twenty days after the last dose of serum the patient was subjected to a test reaction to horse serum—allergic. A dose of 0.25 c.c. of horse serum was injected intradermically over the flexor surface of the left forearm at 10 a. m. The arm was under constant observation for the first ninety minutes following injection. There instantly (from 30 to 60 seconds) developed a small raised white swelling along the needle track and at the point of injection of serum, 1.5 cm. away (Table 3, Case 17 *c*). In four minutes, a well marked hyperemic zone, 4 cm. in diameter, roughly oval in shape, had developed with some swelling. In seven minutes, the swelling was well marked, red and commencing to pit upon pressure. In nine minutes, the swelling was 8 by 4 cm. in diameter, red, tender and painful (typical erysipeloid reaction).

In fifteen minutes, the area had enlarged still more and pitted readily on pressure. A mild grade of lymphangitis developed up the arm; the epitrochlear gland became enlarged and tender.

The swelling enlarged gradually during the succeeding hours, though the color faded somewhat. At 5 p. m. the whole of the flexor surface and part of the radial aspect of the extensor surface was involved.

The patient suffered no constitutional disturbances, no pyrexia, no itching, either general or at the point of injection. The reaction was of a true cellulitis type.

About 2 p. m. of the same day the left thigh commenced to swell and became somewhat tender. Swelling increased for about one hour then gradually subsided.

Thus we have a focal reaction occurring at the site of the injection of serum given three weeks prior to the test dose. It would appear obvious that a definite amount of more or less unaltered serum was present in the muscles of the thigh, and that the balance of tolerance and hypersensitiveness was upset by the test dose, with the result that a reaction occurred in those tissues in which serum from the previous injection still remained.

An experiment similar to that which was carried out in Case 17 was attempted in another case of local tetanus, Case 18.

CASE 18.—Pte. G. B. was wounded Aug. 7, 1917, on which date he received 1,500 units of antitetanus serum.

During the night of August 21 he was disturbed by jumping and slight pain in the left thigh. (He was suffering from a severe compound fracture of the left tibia and fibula.) On August 23, the condition was diagnosed as tetanus. During the ensuing week, he received 90,000 units of antitetanus serum, contained in about 500 c.c. of serum. For the most part, the serum was given locally in an effort to bathe the sciatic and anterior crural nerves. Twenty thousand units were also given intravenously.

After an early tendency of the disease to spread and become more severe, it was well controlled by August 30.

He received no serum after August 29 until September 13, when he was given 0.5 c.c. into the skin on the flexor surface of the left forearm. Absolutely no reaction either constitutional or focal occurred at the site of the previous injections. As the patient's condition at this time was favorable, the tetanus being cured, the pyogenic infection of the wound being well under control, and bony union commencing, he was evacuated to the base.

There are two explanations why, in this case, no reaction, either focal or otherwise, followed the test dose. In my opinion, the absence of reaction was not due to desensitization persisting, but was due to tolerance (immunity) having been established to a degree which was not overcome by the administration of 0.5 c.c. of serum.

The following case is made use of for three separate experiments. In the first place, as the result of the injection of 10 c.c. of serum eighteen months after the last dose in a patient who had previously received repeated doses of horse serum, there occurred a shortening of time and a more severe reaction than usually occurs in previously uninjected individuals. One month later he was found to be extremely sensitive and reacted immediately to a dose of 0.25 c.c. of horse serum given subepidermically. This small dose did not suffice to desensitize the patient, since a focal reaction occurred when he was injected one hour later with a dose of 2 c.c. of serum.

CASE 19.—J. E. H., aged 23, on Jan. 23, 1920, suffered amputation (railroad accident) of both legs. He was brought to the Montreal General Hospital, and immediately operated upon. At the completion of the operation, he was given 1,500 units of antitetanus serum contained in 10 c.c. of serum.

The patient had served throughout the war in France and had been wounded three times. Following these wounds he received five or six prophylactic doses of antitetanus serum. The last dose was administered in August, 1918.

Four days after the injection of serum (Jan. 27, 1920), his temperature suddenly rose to 104 F. (Table 3, Case 19*a*). (Prior to and following this day his temperature had remained about 100 F. at its maximum.) An area of cellulitis appeared on this day over the left deltoid muscle, at which site serum had been injected. This region was slightly itchy and became red, swollen and tender. No joint pains and no evidence of generalized urticaria or erythema was noted.

At 11 a. m., Feb. 21, 1920, he received subepidermically over the flexor surface of the left forearm, an injection of 0.25 c.c. of horse serum (antitetanus serum). Within two and one-half minutes, there was a well established zone of edema, appearing in radiating lines from the point of injection (Table 3, Case 19*b*). Within five minutes a hyperemic zone 5 cm. in width, and 7 cm. in length, had appeared about the injection point. During the ensuing half hour, this increased in size somewhat and became a deep inflammatory red. The whole area was somewhat swollen and tender and was definitely warm on palpation, as compared to the surrounding tissue. Spreading upward from the zone of inflammation, there appeared two parallel lines similar in appearance to those seen in lymphangitis. These reached to the junction of the middle and lower thirds of the upper arm.

The reaction reached its maximum about twenty-five minutes after the injection, and commenced to subside rapidly about eighty minutes after injection. At 1 p. m., 2 c.c. of serum were injected subcutaneously in the upper arm; this area was observed one hour later, at which time a moderate swelling of the part could be palpated (Table 3, Case 19*c*). Obviously, the previous injection of 0.25 c.c. of serum had not sufficed completely to desensitize the patient.

The following day, the patient's temperature, which had been normal during the last week, rose to 100.4 F. This elevation of temperature persisted during the day and the following day. Over the site of the second injection into the upper arm was a slight swelling on both February 22 and 23.

The site of the subepidermal reaction in the forearm, on February 23, consisted of a small elevated area, 1 cm. in diameter, deep red in color, and showing over the center a collection of pus cells (small yellowish gray focus).

The inflammatory nodule on the forearm persisted, though gradually subsiding, for one week. No discharge of pus occurred.

A very interesting feature was the fact that, over the deltoid at the site of the injection, one month previously, there appeared a slight amount of swelling which, however, was not accompanied by itchiness or discoloration of the skin.

Apparently this patient when he received the first dose of the present series was not immune, but had lost to a considerable extent his hypersensitive state. In consequence, however, of his tissues having been previously stimulated by injections of horse serum, anaphylactic bodies developed more quickly than in the normal individual. A reaction occurred, therefore, after a short period. One month after this dose of 10 c.c. of serum, our experiments proved that he was extremely

hypersensitive and also that 0.25 c.c. of serum did not suffice to desensitize.

Abscess Formation.—In several cases, I have observed small collections of pus cells following intradermic injections. The following case is one in which a massive collection of pus developed at the site of serum injection such as occurs more commonly in the rabbit.

Case 20.—The patient, L., following frost-bite, received a dose of antitetanus serum. Seven days later a second dose (5 c.c.) was administered. The second dose was injected deeply into the right rhomboid area; within twenty-four hours pain developed in this area, and the temperature rose to 100.4 F. During the next few days he suffered from anorexia, but no joint pains and no diarrhea.

On the sixth day following the injection, a well marked fluctuating swelling had developed; this remained about the same size until the eleventh day, when it was incised and about 40 c.c. of thick purulent material was evacuated. The operation wound healed at once; there was no reaccumulation of fluid.

From the pus evacuated a few streptococcic colonies were cultivated. These I believe were a contamination from the skin.

Edema of Glottis.—I have not observed any patient showing definite signs of edema of the glottis. The phenomenon is well illustrated by a case reported by Treadgold [8] which is reported herewith:

Case 21.—Pte. P. was admitted suffering from a slight shrapnel wound of the shoulder. This was practically healed on admission, and there was no pyrexia. Symptoms started on the sixth day after the injection of 10 c.c. into the left upper arm. These consisted of a local urticarial rash, which was accompanied by pains in both knees; faintness and giddiness were complained of on getting out of bed, while the temperature rose to 100 F. On the seventh day, the glands in the left axilla were swollen and painful; toward evening the patient vomited twice. Other symptoms remained as before. On the morning of the eighth day, local edema was marked, while the rash had become generalized. There was giant urticaria all over the body, and the itching was intense. Pain was complained of in nearly all the joints, while most of the superficial lymphatic glands were painful and enlarged. At night, the temperature rose to 103.4 F., but the pulse was so feeble and rapid that it could not be counted. There were urticarial spots on the oral mucosa, and the patient was so hoarse that he could hardly speak. Toward evening, the pulse fell to 90 per minute and was stronger. On the tenth day, the hoarseness had disappeared, the temperature was normal and the pulse was much improved, while the rash had practically disappeared. In all, the rash lasted five days, the joint pains six days, and the lymph adenitis seven days.

III. FOCAL AND GENERAL DELAYED REACTIONS

Persons who have not previously received doses of horse serum usually react sometime between the fourth and twelfth days, more especially between the sixth and eighth days, in a fairly typical manner.

8. Treadgold: Serum Disease and Anaphylaxis, J. Roy. Army Med. Corps, **27**:596, 1916.

Some form of rash is the most obvious and regular symptom. The rash is usually urticarial in nature; occasionally it is more erythematous in character, not infrequently simulating the eruption of scarlet fever. In probably all cases there is a febrile reaction during the period of the eruption; it may be high, 103 F. or more; it is more usually between 100 and 101 F. Joint and muscle pains occur, the site of injection is usually sensitive to pressure and the lymph nodes in the vicinity are often swollen and tender.

It is probable that all normal persons react in this way to an injection of 5 c.c. or more. Not infequently the manifestations of the reaction are slight. Serum reactions are diagnosed as such in approximately 80 per cent. of cases.

RÉSUMÉ OF REACTIONS

Following the injection of horse serum into the human tissues various results may be noted, depending on the state of the tissues in relationship to the serum protein.

1. If the individual is normal, no immediate result will be noted. His tissues will be stimulated to elaborate a substance which has the property of altering (splitting [9]) the protein molecule.

The protein splitting substance is gradually developed by the tissues, so that at the end of about six days there is a sufficient quantity available to act on a relatively large quantity of the serum protein. The effect of this cleavage of the protein molecule by the antibody developed by the tissue is that there is liberated a toxic or irritant product.

During that period immediately following the introduction of the horse serum, the amount of available antibody is not sufficient to liberate, at any one time, a sufficient amount of toxic substance to injure the tissues either locally or constitutionally. After the sixth day, the amount of antibody available has reached such concentration that a larger quantity of protein is split. In consequence, the focus in which the

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9. Although in the author's opinion there is sufficient evidence for believing that the manifestations of tissue intoxication or irritation which constitute the phenomena known as anaphylaxis and allergy are due to the formation of a toxic product as the result of splitting or cleavage of the antigenic protein by the serum antibody, it is not his purpose in this article to discuss the nature of the alteration which manifestly takes place. Throughout this discussion of the reaction, as noted in the cases cited, the terms "split-product," "splitting," "cleavage" will be used, even though it is recognized that no proof that the alteration of the protein molecule is, in fact, a cleavage is presented. The author, moreover, desires to point out that the adoption of the hypothesis of the presence of two substances—anaphylactic body and tolerant body—in the tissues of the immune animal or individual is not dependent upon the nature of the reaction—cleavage or otherwise—between the tissue body and the injected antigenic protein.

serum has been injected becomes irritated. As a result of irritation hyperemia develops so that a larger amount of blood is brought in contact with the serum collection. As a result, then, of a greater concentration of protein splitting substance in the body fluids, and an increased circulation through the focus of body fluid containing the serum protein, there is a marked increase in the amount of irritant substances developed. Symptoms of constitutional intoxication then occur. These manifestations consist of fever, skin eruptions, swelling of the synovial membranes with consequent joint pains, and occasionally nausea or vomiting and diarrhea.

At the site of serum injection and in the neighboring (or distant) lymph nodes, evidences of inflammation such as hyperemia, interstitial edema, pain and tenderness, are noted.

2. If the individual is hypersensitive to horse serum, either because he has previously received parenteral injections of horse serum, or from any other cause, the injection of horse serum into his tissues is immediately followed by a reaction between the protein splitting substance already present and the injected protein.

The severity of the reaction which takes place will depend upon several factors:

(*a*) The degree of sensitiveness of the patient.

(*b*) The route of injection (intradermic, subcutaneous, intramuscular, intrathecal or intravenous). This is important, since depending on the nature of the tissue into which the serum is injected, there will be a variation in the available proportion of the total amount of protein splitting substance (anaphylactic antibody) present in the body.

(*c*) The amount of serum injected.

(*d*) The rate of injection. If the serum is very slowly injected into the blood stream, the total amount of protein splitting body available may be exhausted by a very small amount of serum. The amount of serum which is capable of absorbing all the available antibody may not be able to supply a sufficient quantity of toxic splitting protein materially to injure the individual.

(*a*) If the individual is very sensitive, if the route of injection is intravenous, and the dose injected sufficient to produce an active amount of toxic split protein, there occurs almost instantaneous liberation of the toxic product, with immediate manifestations of grave intoxication of the individual. Death may supervene within a comparatively few minutes, either as the result of drop in blood pressure and arrest of circulation, as is seen in anaphylactic shock in the dog, or the reaction which occurs is respiratory, as in the guinea-pig. In the human being,

it would appear that this respiratory type of reaction, though very terrifying, is less likely to lead to a fatal outcome than is the splanchnic reaction.

In a certain proportion of patients that are shocked by the parenteral introduction of serum, there occurs, as has been previously mentioned, a recurrent splanchnic reaction, after the lapse of several hours, which may prove fatal.

The explanation of this delayed reaction is by no means a simple one. It is my opinion that death in such a delayed reaction is due to the formation, more especially in the duodenal mucosa, of a toxic substance similar to that found by Whipple and his associates [10] in cases of duodenal obstruction and demonstrated by myself [11] to be formed when the portal venous circulation is obstructed. It is probable that, in consequence of the splanchnic congestion with its resulting venous stasis in the duodenum, nutrition of the mucosa of the duodenum is interfered with, to a degree which suffices to permit the formation of a toxic substance.

(*b*) If the serum is injected intradermically in small quantities, for example 0.25 c.c., the reaction which occurs is almost entirely focal. It commences within two or three minutes, or less, and is characterized by a well marked cellulitis of the tissues surrounding the injectetd area, accompanied not infrequently with lymphangitis, and lymphadenitis.

(*c*) If the serum is injected intramuscularly, it is brought in contact with less blood than if given intravenously. In consequence, the reaction which occurs is, other things being equal, less severe and more prolonged than following intravenous administration, though more severe than following intradermic injections.

3. If the individual has been desensitized by a recent injection of horse serum (a few hours to four days previously) the injection of a subsequent dose will find the tissues free from any available anaphylactic (protein-splitting) body. In this event, the injected serum will not be immediately split, as is the case in the hypersensitive individual, but will remain unaltered pending the accumulation, through the activity of the tissues, of a fresh supply of protein-splitting body. Since the tissues have already been stimulated to produce the antibody, the development of amounts sufficient to cause the liberation of an amount of split protein capable of injuring the tissues requires a shorter period than in the normal individual. In consequence, the outbreak of clinical manifestations of irritation will not be delayed for eight or nine days, but will appear at the expiration of a shorter interval.

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10. Whipple, Stone and Bernheim: J. Exper. M. **17**:286, 307, 1913.

11. Gurd, F. B.: The Toxins of Intestinal Obstruction, J. Infect. Dis. **15**: 124, 1914.

4. If the person has received frequent large doses of serum within a few weeks or months, he will be to a certain extent immune (tolerant) to the toxic effects of the splitting of the serum protein. Such a patient may be injected by any route with a small dose of serum, without the development, either immediately or later, of manifestations of intoxication. In such a case the injected serum protein is split, but there is also present in the tissues a substance which is capable of neutralizing the toxic split-protein.

It is not deemed advisable in this article to enter into a consideration of the nature of the substance responsible for this neutralization of the toxic protein. A theory,[12] which in my opinion is supported by a certain amount of evidence and which suffices to explain the various phenomena noted, is that there is developed, as a result of previous stimulation of the tissues by sublethal doses of the split protein, a second type of body capable of further degrading the protein molecule to the stage of the polypeptids or amino-acids.

It is readily proved by means of experiments of transferred anaphylaxis[13] that there is, at all times, available in the tissues of protein-immune animals an amount of anaphylactic body greatly in excess of the amount of immune body. If, therefore, the amount of serum injected is potent to produce a greater amount of toxic split protein than can be neutralized by the available tolerant body, immediate manifestations of intoxication, as in the sensitized individuals, will occur.

The fact that it is possible to inject hypersensitive individuals with a small dose of the protein to which they are hypersensitive, without the development of toxic symptoms, must be borne in mind. Should the injection of a test dose in an individual suspected of being hypersensitive, either as a result of his being asthmatic or in consequence of his having previously received injections of horse serum, prove negative, the evidence thereby gained should not be accepted as final. The person should again be injected with a second test dose, larger in quantity, before it is assumed that he is not hypersensitive.

In my opinion, the fact that the hypersensitive individual may also be tolerant to the toxic split protein and consequently his hypersensitiveness may not be evident if too small an amount of the test serum is introduced is an important argument against the exclusive employment of the cutaneous method of testing for hypersensitiveness as used by Walker and others. By the employment of the subepidermal method

12. Gurd, F. B.: Anaphylaxis and Allergy and Their Relationship to Immunity, Am. J. Trop. Dis. and Prevent. Med. **1**:776, 1914.

13. Gurd, F. B.: Studies Upon Anaphylaxis and Its Relationship to Immunity, Am. J. Trop. Dis. and Prevent. Med. **1**:776, 1914.

of injection, more clean cut reactions are induced, and the quantitative element which is lacking in the cutaneous method is obtained. The method, moreover, is of real value in commencing desensitization of the individual.

DETERMINATION OF HYPERSENSITIVENESS AND DESENSITIZATION

At the present time, there are not sufficient data available to permit one to state with positiveness the optimum dosage of horse serum which should be employed in the determination of hypersensitiveness or in the induction of desensitization. I have employed a method which has apparently proved satisfactory although in one case (Case 9) the amount used was excessive. For the test dose, 0.25 c.c. of serum is introduced subepidermically. In performing the test, I have been accustomed to employ a very fine needle which is introduced through the skin and made to penetrate the skin again at a distance of a centimeter or more from the original puncture. As soon as the point of the needle is visible through the epidermis, serum is injected. In this way, a small white wheal is formed, which is the center of the subsequent reaction. *It is of the utmost importance that the fluid should not enter a vein.* Such an accident can be guarded against by attempting to withdraw the plunger of the syringe before injecting the fluid.

In sensitive individuals, the reaction commences almost immediately (from twenty to one hundred and eighty seconds), and consists in its first stage of an enlargement of the original wheal, usually in a radiating manner. Not infrequently at this stage, the point becomes itchy. Surrounding the definitely raised area, there appears within from three to five minutes a hyperemic zone, 1 to 5 cm. in diameter, which rapidly increases in size until it attains its maximum size, about one-half hour after injection.

Case 18 proves that in certain hypersensitive individuals, for such this patient must be considered to have been, 0.25 and even 0.5 c.c. is too small a dose to prove hypersensitiveness in individuals who have recently received large doses of serum and who are in consequence tolerant.

Should there be no reason for suspecting the patient to be highly sensitive or perhaps tolerant, a negative reaction to this amount (0.25 c.c.) may be accepted as proof that the individual is not hypersensitive in an important degree. On the other hand, should the fact that the patient had recently received one or more doses of serum lead one to suspect that he might be both hypersensitive and tolerant, the injection should be repeated about one hour after the first, a larger quantity, 1 to 1.5 c.c. of serum being employed.

Should a well marked reaction occur following the test dose, within one or two hours, a larger dose, 1.5 to 2 c.c., should be injected before assuming that the patient is desensitized. *That it is possible to inject a hypersensitive individual with serum in the hope of desensitizing him with a dose which is too small to exhaust all the available anaphylactic bodies must be remembered.* This is shown by the effect of a second injection two hours after the first injection in Case 19.

Even though repeated intradermic and subcutaneous injections have been made and desensitization believed to have been obtained, the greatest care should be taken in performing intravenous injections in patients who have reacted to the test dose. The serum injected should be diluted one in twenty of saline solution and allowed to run into the vein very slowly (Besredka).

TREATMENT

In the treatment of the mild forms of the reaction, little is necessary. In my experience, the discomfort arising from the urticaria is usually relieved by the administration, either before or after its development, of calcium lactate or chlorid, followed by a dose of magnesia. I have been accustomed to give the patient a mixture containing 1 dram of calcium chlorid, one fourth of the mixture to be taken every fifteen minutes; and at the end of the hour a dose of 4 drams of milk of magnesia is given.

In the treatment of the severe cases of splanchnic dilatation, posture, including compression of the abdomen, should be employed. Fluids, probably best in the form of hypertonic glucose (10 per cent.) solutions or gum acacia, are administered intravenously. Epinephrin, in doses of 5 or 10 minims (1:1000) intravenously, should be employed, if available, for its splanchnic effect. In the event of a recurrence of symptoms, further injections of epinephrin must be employed.

Although probably less effective than suprarenal extract, pituitary extract is, I believe, of value. It is probable that although its effect is less prompt than epinephrin, the best results are obtained by employing the latter preparation intravenously and injecting the pituitary extract in doses of 1 c.c., subcutaneously.

In cases of respiratory reaction, epinephrin should also be employed and, in addition, oxygen should be administered. As suggested by Auer and Lewis, the effect of atropin upon the smooth musculature is of real value in relieving the dyspnea. This drug should be administered in doses of 1/100 grain. In view of the fact that animals are apparently more resistant to fatal shock when under the influence of anesthesia and in view of the excellent results obtained by Munro in his case, chloroform or ether may well be administered. Artificial respiration should always be employed.

SUMMARY

The clinical phenomena which are grouped under the heading of serum sickness are manifestations of intoxication or irritation of the body tissues as the result of an alteration in the character of the injected serum protein molecule. This alteration of the molecule is due to the activity of specific substances presented in the tissues and body fluids. The stimulation necessary for the elaboration of such specific substances is a previous exposure of the tissues to the same protein.[14]

The alteration which takes place in the injected protein molecule (perhaps a cleavage of the molecule) results in a product which is extremely irritating to the tissues, more particularly to the involuntary muscles.

The animal or individual whose tissues are hypersensitive to a specific protein is said to be anaphylactic. When the reaction which occurs as the result of the interaction of injected protein and anaphylactic substances takes place in fulminant fashion, the phenomenon has been known by laboratory workers as anaphylactic shock. When, in consequence of either incomplete hypersensitiveness, small dosage, or gradual exposure of the injected serum to the anaphylactic bodies, the reaction is more gradual in onset and less severe, the condition is sometimes referred to as subacute anaphylaxis. In the human being, it is this less severe and more gradual type of reaction which is more usually encountered. The term allergy (von Pirquet) is ordinarily reserved to designate the focal visible reaction which occurs at the site of the introduction of the protein antigen in sensitive individuals. The manifestations as ordinarily seen in the human being are:

1. An inflammatory reaction (mild to moderately severe cellulitis) at the site of injection. This may be accompanied by lymphangitis and lymphadenitis.

2. Pyrexia, with accompanying headache and anorexia, and accelerated pulse rate.

3. Skin eruptions, commonly of an urticarial or erythematous type.

4. Joint pains, presumably due to swelling of the synovial membranes.

5. Occasionally, though rarely, accompanying the general urticaria and edema of the skin, edema of the larynx may occur.

6. Albumin is probably present in the urine for a short period in nearly all cases, though on this point sufficient data are not available.

14. From time to time, cases are seen in which it is impossible to determine the time at which such exposure occurred.

7. Leukocytosis, which may be marked, is present during the stage of pyrexia. (When the reaction occurs immediately after injection leukopenia is noted.) It is not improbable that a similar leukopenia occurs early in the reaction period in cases which later show a leukocytosis.

In hypersensitive individuals, an immediate reaction takes place. The manifestations of this immediate reaction are:

1. The focal inflammatory reaction at the site of injection is more severe, and occasionally results in suppuration or even necrosis of tissue.

2. There is often a feeling of fulness or pain in the epigastrium.

3. Vomiting and diarrhea, the latter often bloody, take place.

4. There may be marked splanchnic dilatation as evidenced by collapse, drop in blood pressure, and tachycardia. Examination of the blood reveals concentration. Such an effect may result in a complete arrest of circulation and death of the patient.

5. There may be marked dyspnea, accompanied by cyanosis and a choking sensation. Death may supervene from arrest of respiration.

In exceptional cases following an immediate splanchnic reaction with subsequent, more or less complete apparent recovery, there may occur after the lapse of some hours a recurrence of the collapsed state which may end in death.

Hypersensitive individuals may be desensitized so that large amounts of serum may be injected without danger. The method of desensitization that I employ has been heretofore described.

Avoidance of reactions is of greater value than is treatment. In all suspicious cases, prior to the injection of serum for prophylactic or therapeutic purposes, the absence of hypersensitiveness should be proved by means of an intradermic test. If found to be sensitive, the individual must be desensitized.

Treatment, in the event of severe reactions, must be promptly undertaken and pushed to the utmost. The various procedures which have apparently proved their value are discussed in the body of this paper.

THE RELATION OF MULTIPLE VASCULAR TUMORS OF BONE TO MYELOMA

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From time to time articles have appeared discussing vascular tumors arising in the bones, which have presented peculiarities resulting in their designation variously as pulsating sarcoma, bone aneurysms, hemangio-sarcoma and hemangio-endothelioma, a variety of terms which indicate either that several different pathologic conditions may present similar characters, or that a single condition presents different features at different times and places.

The present consensus seems to be that true bone aneurysms rarely, if ever, occur, and that most, if not all, of the growths under discussion represent merely malignant neoplasms with hemorrhagic softening. Oehler early noted that in such cases the tumor tissue might be difficult to find, persisting merely as a thin superficial layer. He assumed that the so-called bone aneurysms arise from hemorrhagic sarcomas of bone, the blood stream gradually washing out the sarcoma cells. Gaylord [1] accepted this view, reporting a case in which only a small area presented tissue that could be interpreted as sarcoma. He stated that small, thin-walled blood vessels ran through the structure, and the illustrations and descriptions recall the appearance of organizing clots. He recognized that repeated hemorrhages might destroy the sarcoma, and so possibly lead to a spontaneous cure. Nakayama [2] agreed that the hemorrhagic-cystic sarcoma arises from a solid tumor altered by hemorrhage into the tumor tissue. He said that the sarcoma is usually of a mixed form with no predominance of any cell type, but he believed that there are also bone aneurysms that do not originate from sarcoma.

Howard and Crile [3] reviewed eighteen cases reported as endotheliomas of bone and added five more. Several of these had been mistaken for bone aneurysms. It is to be noted that in at least thirteen of these cases, the tumors were multiple, the bones of the skull, vertebrae, sternum, ribs and femur being most often involved, wherein they resemble the multiple myelomas, as well as in a lack of visceral metastases. Although albumosuria was not reported in these cases, it was probably not particularly sought.

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1. Gaylord: Ann. Surg. **37**:835, 1903.
2. Nakayama: Beitr. z. klin. Chir. **64**:524, 1909.
3. Howard and Crile: Ann. Surg. **42**:358, 1905.

Ewing [4] accepts the occurrence of true endotheliomas of bone, stating that the structure presents thin strands of connective tissue supporting one or more layers of large clear cells enclosing spaces sometimes containing blood. He mentions, however, that "in one case, besides the clear cells, there were some areas resembling plasma cells." In discussing Marckwald's case of "geniune endothelioma" with multiple tumors in the flat bones, he says; "The general condition represented multiple myeloma, but the structure of the growth was entirely different;" and also, "Marckwald analyzed several cases from the

Fig. 1.—Vascular channels with some tumor cells persisting in proximity thereto; ×85.

literature. Some of these, however, were clearly multiple myelomas." He concludes that "while uncertainty still surrounds the origin of these tumors of the bone marrow, it is not clear that they can be separated from multiple myeloma."

Symmers and Vance [5] have reported an interesting case of this category under the explanatory title "Multiple Primary Intravascular

4. Ewing: Neoplastic Diseases, 1913, p. 313.
5. Symmers and Vance: Am. J. M. Sc. **152**:28 (July) 1916.

Hemangio-Endotheliomata of the Osseous System Associated with the Symptoms of Multiple Myelomata—A Lesion Hitherto Undescribed." In this case several of the flat bones and the upper end of the humerus were involved, but two examinations for Bence-Jones protein were negative. As no necropsy was performed, the only material available for study was that obtained by curetting a tumor attached to the ischium. The description of the histologic appearance was as follows:

The unit of the tumor is a thin-walled blood vessel, lined by a single layer of flattened endothelial cells, the lumen distended by red blood corpuscles,

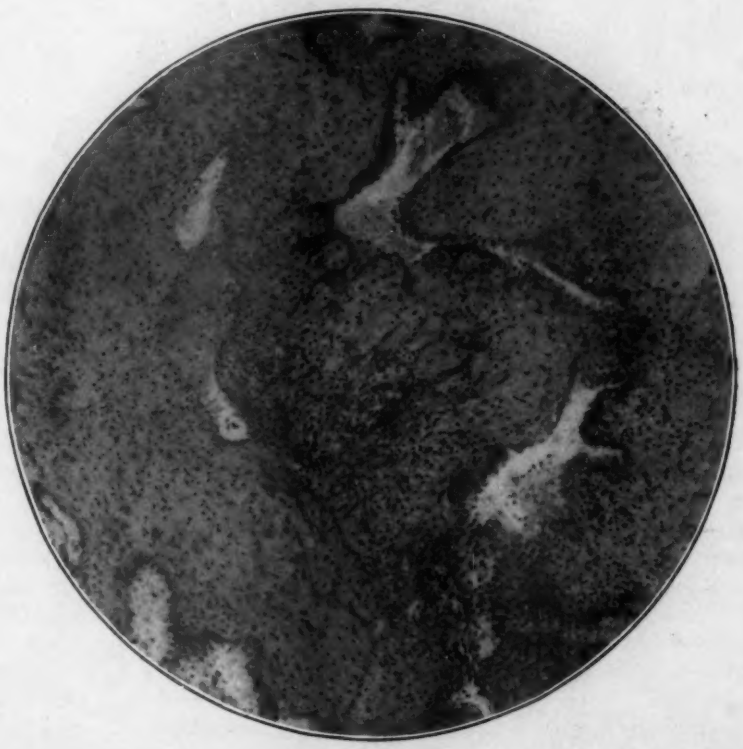

Fig. 2.—The predominating type of tissue, consisting of large blood channels with one or several layers of large endothelial cells and a cellular, edematous intervascular tissue; ×75.

the whole embedded in a stroma of poorly cellular fibrillar connective tissue arranged around spicules of bone. Here and there, however, the lining endothelium may be seen as a uniformly growing circumferential layer from five to twenty cells in depth, and from this point the process of proliferation may be followed through various stages leading to occlusion of the lumen by spindle-shaped tumor cells. In other cases, the overgrowth of endothelium commences at the periphery of the vessel as one or more armlike projections and the lumen is eventually occluded. An extraordinary histologic feature con-

sists in proliferation of the endothelium in such a way as to subdivide the vascular lumen into one or more compartments filled by red cells, obviously representing an attempt to form new vascular channels.

That true hemangiomas of bone may occur, if rarely, is indicated by Trommer's [6] compilation of eight cases, including one of his own, which seem for the most part to answer to this designation. Especially well established are those cases in which typical hemangiomas were also found outside the bones.

Fig. 3.—High magnification of vascular channel and intervascular tissue; × 115.

I have studied a case belonging to the group of vascular tumors of bone, which has seemed to explain certain features of the striking and peculiar angiomatous character of these growths.

REPORT OF CASE

History.—A Lithuanian laborer, aged 45 years, was admitted to Cook County Hospital, Dec. 22, 1917, stating that he had been well until three months previously (five months before his death) when he began to be troubled with pain in the right lumbar region, which soon extended to the left side

6. Trommer: Frankf. Zeit. f. Path. **22**:313, 1920.

also. This pain was exaggerated by exertion, bending and defecation. About this time his legs also became painful and swollen to the knees, so that he was obliged to remain sitting in a chair for three weeks. He then felt better and went back to his work, which involved lifting heavy boxes. After working two days, while lifting a box, he suddenly felt something crack and give way in his back. He was obliged to go to bed where he had since remained, unable to move his legs without discomfort, and with some difficulty in emptying his bladder. Immediately after this incident, he noticed a swelling in his back, which had not increased in size. For the three weeks preceding admission, he had a dull aching pain in the chest, associated with a sense of constriction. No other points of significance are recorded in the history except that he had been a heavy drinker.

Physical Examination.—This revealed slight edema of the feet, slight enlargement of the prostate, and a separation of the left rib from the spinal column with some loss of bone tissue. At this time, the reflexes were normal.

After four weeks he developed paresis of the lower extremities, with loss of reflexes and positive Babinski and Chaddock signs on both sides. The spinal fluid was clear, with a yellowish tinge (xanthochromia?) and an abundance of globulin. The Wassermann reaction was negative with both spinal fluid and blood. The urine was reported as normal, but was not examined specifically for Bence-Jones protein. The blood was normal. No other findings of importance were recorded, except a febrile attack in January, when his temperature rose to 105 F. The clinical diagnosis was neoplasm involving the eleventh rib on the left and the lower dorsal vertebrae with pressure on the cord.

Necropsy Findings.—The patient died in the hospital, Feb. 13, 1918, and the body was examined on the same day.

External examination showed a slight protrusion about the base of the eleventh left rib, and some induration about the end of the twelfth left rib, without adhesion to the skin. Beyond slight edema over the ankles and a slight enlargement of the lymph glands in the left groin, no other external abnormalities were found. The large serous cavities were without important changes. The heart was slightly hypertrophied, with a terminal dilatation of the right ventricle. The blood vessels were practically free from sclerosis. The lungs showed only a slight hypostatic edema, and a laminated thrombus in one of the large arteries in the left lower lobe. No gross signs of tuberculosis were found. The kidneys showed slight chronic nephritis, with an early acute infection, probably ascending from the bladder, which showed a marked acute cystitis, without prostatic changes. The perirenal tissues on the right side were indurated and firmly adherent to the kidney. Otherwise, there were no gross visceral changes.

On the posterior surface of the sternum, at the level of the third rib, on the left side, there was a small area where the bone was twice the normal thickness. When cut with the necropsy knife, no soft tissue was found, the thickening being solid bone growth.

The vertebral column showed a marked lordosis in the lumbar region, with a kyphosis in the lower dorsal region.

The eleventh and twelfth ribs on the left side had apparently lost their attachment to the vertebral column. At the attachment of the eleventh left rib to the vertebra, there was a retropleural, fluctuating swelling, and there

was an increased amount of soft tissue in this location which extended from the tenth to the twelfth dorsal vertebrae.

In the neighborhood of the swelling, there was hemorrhage into the surrounding tissue and a complete solution of continuity of the eleventh left rib, with a gap about 4 cm. long, containing a soft, friable, dark red tissue. The body of the eleventh vertebra was somewhat eroded, and almost completely replaced by a soft jelly-like tissue that greatly resembled a blood clot, although of a somewhat firmer or tougher texture; the vertebral column at this point was easily cut into by an ordinary necropsy knife.

The body of the third lumbar vertebra showed similar invasion by like tissue, as did also the fifth dorsal vertebra at its attachment to the fifth right rib, extending into and involving the fifth right rib to such an extent that a finger could be inserted between the eroded end of the rib and the vertebra.

To the right of the median line, opposite the fifth dorsal vertebra, there was a small subpleural nodule, which appeared to be a pleural metastasis; in this vicinity there was also an independent area of diffuse growth of a distinctly neoplastic nature, whitish in color, measuring 3 cm. square by 0.5 cm. thick.

Microscopic examination of the viscera revealed nothing that was not indicated by the gross examination, except the presence of much hemosiderin in the spleen, and some fatty infiltration and round cell proliferation in the liver.

STRUCTURE OF THE BONE TUMORS

Microscopically the soft tumor tissue outside the bones, including the pleural and subpleural nodules,[7] exhibits the typical features of myeloma of the myeloblastic type, corresponding therefore to the clinical and gross anatomic picture of multiple myeloma of the flat bones.

On the other hand, the bloody or gelatinous growths found in the bones presents an entirely different picture, and indeed it is difficult to find within the bones any tissue resembling the myelomatous growth. About all that remains of the original intra-osseous tumor growth are occasional small islands of myeloblastic cells. Often these persist about the new-formed blood sinuses in large areas of hemorrhagic necrosis, thus suggesting a hemangiosarcoma or a perivascular endothelioma (Fig. 1). However, the amount of myeloma tissue left within the bone is so small that it would be difficult to identify this as a case of multiple myeloma if it were not for the extra-osseous infiltration and the pleural metastases. Had the patient died without extra-osseous growths, as commonly is the case in multiple myelomatosis, the diagnosis would probably have been that of primary multiple vascular tumors of the bones, with uncertainty as to whether this was to be interpreted as an endothelioma or a hemangiosarcoma.

The intra-osseous tumor tissue presents many different features in different sections, passing from the areas where some myeloma tissue still persists in areas of hemorrhagic necrosis, through all the stages

7. The occurrence of true metastasis of myelomas outside the bones has been discussed by Symmers, Ann. Surg. **67**:687, 1918.

of organization of a blood clot until areas can be found where there remains still living bone with its marrow replaced by loosely organized connective tissue with more or less blood pigment, and few or no cells characteristic of bone marrow. Apparently these last named areas, which are found in the intact bony shell about the vascular tumors, represent complete hemorrhagic necrosis and replacement of the peripheral tumor tissue, destroyed by pressure against the intact bone.

A large proportion of the intra-osseous neoplastic tissue, which formed the red, jelly-like masses, consists of organizing clot with wide blood channels, and an intervascular framework of edematous embryonal tissue (Figs. 2 and 3). In some places, this assumes the appearance of myxomatous tissue, in others of a spindle-cell growth suggesting somewhat sarcoma. There are considerable areas in which masses of very large pale cells form the matrix beween the vascular channels, and these seem to correspond to some of the descriptions of endotheliomas in bones, but probably are embryonal cartilage cells. Most of the blood sinuses are lined with cuboidal embryonal endothelium, which is often heaped up into several layers or into nodules, thus intensifying the resemblance to endothelioma. Occasional myeloblastic cells are found in this vascular tissue, enhancing its apparent neoplastic character.

SUMMARY

From the gross and microscopic standpoints, therefore, we find in this case illustrations of two different pathologic processes in the involved bones. Although unquestionably the condition is actually one of multiple myelomatosis of the bones, yet there are features that seem to correspond perfectly to what have frequently been described as either angiosarcoma or multiple endothelioma of bone. If one were presented only with sections of the bloody, gelatinous tumors within the bone, there would be found nothing to suggest the existence of a myeloma, and with some of the sections the diagnosis of hemangio-endothelioma would be strongly suggested. Therefore, *a growth that begins as a myeloma may take on the characteristics of a neoplasm of vascular origin, with no remnants of the original tumor to be found in the entire bone tumor.* It would seem probable that this is the explanation of the case reported by Symmers and Vance, and that necropsy would have disclosed that it really was a case of multiple myeloma.

As an explanation of the production of these highly vascular growths of embryonic type of blood vessels replacing tumors in the bones, these points may be advanced: Because of the unyielding character of the osseous shell of the bone-marrow tumors, the growth of the tumor cells is more likely to shut off the blood supply and to produce necrosis than is the case in tumors located in other tissues. Following the

necrosis, hemorrhage replaces the absorbed material, and organization of the resulting clot takes place. But, again, because of the firm outer shell of intact bone, the organization does not follow the course usual in organization in other tissues, for the contraction and obliteration of the capillaries cannot take place. Instead, the new connective tissue becomes more or less edematous or of a myxomatous type, since it cannot contract to form scar tissue, and the new-formed vessels persist in their large embryonal form, or even dilate with absorption of the clot, and later secondary proliferative changes of the intima of these blood channels may still further enhance the resemblance to an endothelial neoplasm. Such changes are not peculiar to hemorrhagic tumors in bones, for they may be observed in greater or less degree whenever vascular granulation tissue is prevented from contracting because of its attachment to bones, for example, in some areas of organizing pleural exudates close to the ribs, or in the floor of leg ulcers overlying the tibia.

The observations lend support to the opinion expressed by others, notably Ewing, that many of the tumors described as multiple vascular endotheliomas of bone, and sometimes also as bone aneurysm, are really myelomas. This view is in harmony with the fact that myelomas are the chief form of multiple bone tumors, and that the frequency, if not the existence, of true endothelioma, is becoming less and less supported. It is, of course, probable that other bone tumors than myelomas may undergo the same sort of hemorrhagic necrosis and replacement by vascular new tissue.

THREE CASES OF SUBPERITONEAL, PEDUNCULATED ADENOMYOMA *

THOMAS S. CULLEN
BALTIMORE

Adenomyomas of the uterus are becoming more and more frequently recognized.

The diffuse adenomyoma may begin in the anterior or posterior wall of the uterus, but not infrequently the growth forms a definite mantle around the uterine cavity. In time portions of it may be forced into the cavity of the uterus forming submucous adenomyomas, which occasionally are expelled through the cervix.

In other cases a portion of the diffuse adenomyoma may be forced to the outer surface of the uterus, producing a subperitoneal or intraligamentary adenomyoma. Such growths are not very common. I have discussed subperitoneal and intraligamentary adenomyomas of the uterus so fully in a previous publication [1] that it would be mere repetition to go into details in the present paper.

During the month of November, 1920, I operated upon three different patients for subperitoneal, pedunculated adenomyoma. In Case 1 the condition was detected in the laboratory, in Cases 2 and 3, the diagnosis became perfectly clear as soon as I had exposed the subperitoneal tumor that lay in the pelvis.

These three cases are such beautiful examples of a relatively rare condition that we may with profit consider them in detail.

The drawings by Mr. Brödel, supplemented by the photomicrographs by Mr. Schapiro, tell nearly the whole story, consequently this paper may be considered merely an accompaniment to their splendid artistic rendition.

REPORT OF CASES

CASE 1.—*Multiple uterine myomas; adenomyoma of the anterior uterine wall densely adherent to the bladder; diffuse adenomyoma of the posterior uterine wall with a pedunculated, subperitoneal adenomyoma springing from it* (Figs. 1, 2, 3 and 4).

History (Gyn. No. 26282).—S. J., colored, aged 39, was admitted to the gynecologic department of the Johns Hopkins Hospital, Nov. 2, 1920. Novem-

* From the gynecologic department of the Johns Hopkins Medical School and of the Johns Hopkins Hospital.

1. Cullen, T. S.: Adenomyoma of the Uterus, Philadelphia, W. B. Saunders Company, 1908, Chaper 5, p. 125 et seq.

ber 4 she was transferred to the medical service on account of her cardiac condition. She was readmitted to the gynecologic service, Nov. 9, 1920 (Gyn. No. 26340). Two of her sisters had died of tuberculosis. She had had a dry pleurisy at 30, but otherwise had been healthy. Her menstrual flow ceased completely for one year when she was 18. As a general thing, it had been scant, lasting from two to three days, now it was profuse and was of four to five days' duration. There was no intermenstrual bleeding. The patient was unmarried and had never been pregnant.

In May, 1920, she began having pain in the lower part of the back at the periods. It radiated around to the front, there being discomfort in the lower abdomen particularly on the left side. She had had some nausea and vomiting. During the last two months, the patient had developed shortness of breath and had had insomnia.

Physical Examination.—Her eyes showed interstitial keratitis. The heart was not enlarged, but there was a systolic murmur at the apex which was transmitted to the axilla, and there was an extra systole every third beat.

Partially filling the lower abdomen was an irregular growth. On pelvic examination, a rough, firm, irregular mass was found filling the posterior fornix. This tumor extended upward almost to the umbilicus and laterally reached the crest of the ilium. Arising from the left lateral wall of the vagina was an irregular polypoid growth which appeared at the outlet.

Operation.—Nov. 10, 1920, I performed a supravaginal hysterectomy in the usual manner. Some difficulty was experienced in liberating the bladder, which had become densely adherent to a small myoma situated in the anterior wall of the uterus. The left tube and the appendix were removed with the uterus.

The postoperative convalescence was uneventful and the patient was discharged on the fourteenth day.

Examination of Specimen (Gyn.-Path. No. 26352).—The specimen consists of a myomatous uterus with the left tube and ovary attached (Fig. 1).

The supravaginally amputated uterus is 10 cm. in length, 13 cm. in breadth and 9 cm. in its anteroposterior diameter. Scattered throughout the walls of the uterus are several interstitial and partly submucous myomas. The largest of these is approximately 6 cm. in diameter.

On the anterior surface of the fundus is a sessile nodule, 3 by 1.5 cm. This myoma was covered by adhesions. On splitting it, the cause is found to be evident. The upper portion consists of a discrete myoma, the lower portion of a diffuse myoma, irregular in outline, 1.5 cm. in length, which contains two small brownish areas each about 2 mm. in diameter. This small diffuse growth is without a doubt an adenomyoma.

The cavity of the uterus is 5.5 cm. in length. Its mucosa does not seem to be altered.

Springing from the posterior surface of the fundus is a spherical myoma, 3 cm. in diameter. Its pedicle is unusually well developed, and measures approximately 1 cm. in length and 7 mm. in diameter. This myoma on section presents in most places the usual appearance, but at several points are small areas presenting the typical chocolate-colored appearance. These areas vary from 1 to 2.5 mm. in diameter.

The left tube and ovary offer nothing of interest.

Histologic Examination.—Sections from the endometrium show an intact surface epithelium. The mucosa looks perfectly normal, but here and there it extends into the underlying muscle. The muscle presents a diffuse myoma-

tous appearance. Scattered everywhere throughout the posterior wall of the uterus over a wide area and particularly pronounced in the vicinity of the pedunculated nodule noted on the posterior surface are many areas of uterine mucosa. The picture as a whole is one of a definite diffuse adenomyoma of the posterior uterine wall. In some places individual glands are found in the muscle. Some of these lie in direct contact with it, others are separated from it by a small zone of stroma. Here and there are miniature uterine cavities. Many of the glands are dilated.

The small discrete myoma noted in the anterior wall of the uterus shows a considerable amount of hyaline transformation. The diffuse myomatous thickening beneath this myoma contains uterine glands and also two miniature

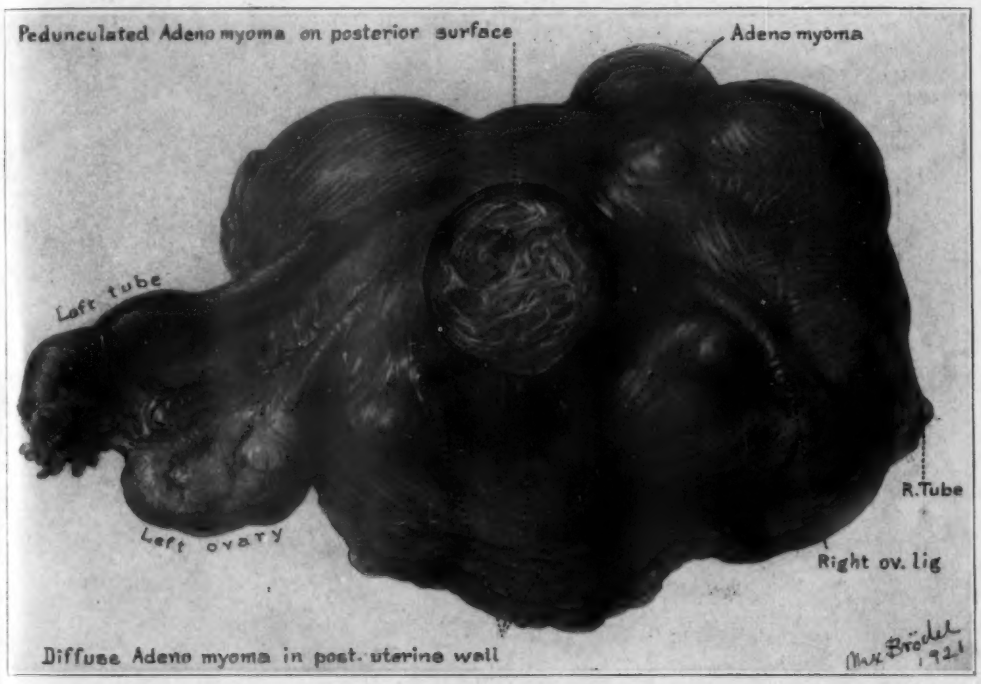

Fig. 1 (Case 1).—A pedunculated adenomyoma springing from the posterior surface of the uterus (Gyn.-Path. No. 26352). Scattered throughout the uterine walls are numerous interstitial and subperitoneal myomatous nodules. In the anterior wall just beneath a myoma, and at a point indicated by the arrow, was a small diffuse adenomyoma. To this the bladder was densely adherent. The posterior uterine wall is occupied by a very extensive diffuse adenomyoma. Springing from this area is a pedunculated myoma. On section this is seen to contain several small cavities in its upper portion. The histologic appearances of this pedunculated myoma are shown in Figures 2, 3 and 4. The cystic areas which were filled with chocolate-colored material are miniature uterine cavities. Islands of uterine mucosa were also scattered throughout the myoma.

uterine cavities, both of which contain a small amount of blood. These are the cavities that were filled with chocolate-colored material. It was at this point that the bladder was densely adherent at the time of operation.

The pedunculated subperitoneal myoma springing from the posterior surface of the uterus consists of typical myomatous tissue, very dense in character. At one point just at the surface of the myoma is an especially dense area, 5 mm. long and varying from 2 to 3 mm. in breadth (Fig. 2). This stains very deeply and consists of myomatous tissue. It contains a definite miniature uterine cavity and a large area of typical uterine mucosa, the stroma of which shows old blood (Fig. 3).

In the depth of the myoma there is a definite miniature uterine cavity (Fig. 4). Lining one side of this is the characteristic uterine mucosa, which shows some hemorrhage. The greater part of the cavity is lined with flattened epithelium lying in direct contact with the muscle. This miniature uterine cavity contains exfoliated epithelium, a few polymorphonuclear leukocytes and some blood. The tumor is a pedunculated subperitoneal adenomyoma.

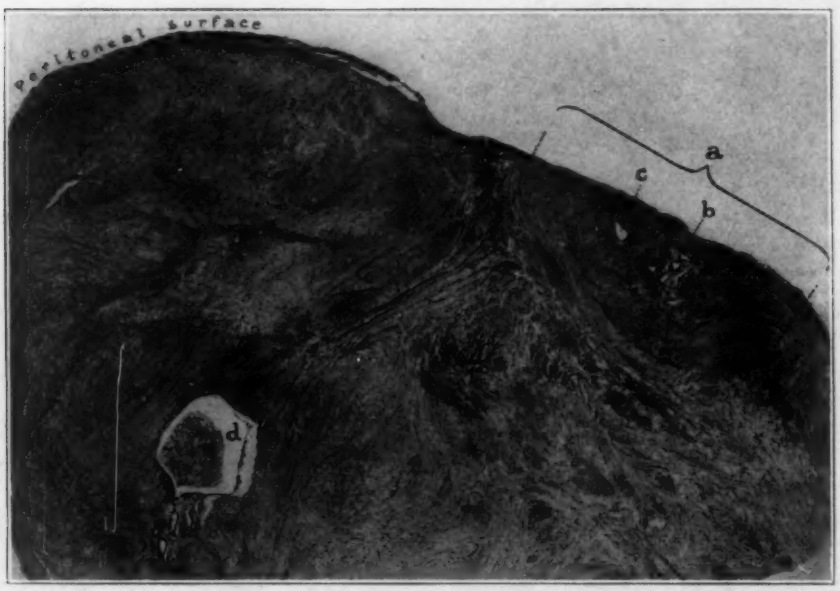

Fig. 2.—A subperitoneal pedunculated adenomyoma of the uterus (Gyn.-Path. No. 26352). This is a very low power picture of a portion of the pedunculated myoma springing from the posterior surface of the myomatous uterus seen in Figure 1. At *a* is a sharply circumscribed myomatous area. Just beneath the peritoneal surface it contains an island of typical uterine mucosa (*b*), also a miniature uterine cavity (*c*). An enlargement of this area is shown in Figure 3. In the lower left part of the field is another miniature uterine cavity *d*. An enlargement of this is shown in Figure 4.

When we consider the specimen as a whole, we find that the endometrium shows a definite tendency to extend downward. Myomatous nodules are scattered throughout the uterine walls. There is a diffuse adenomyoma in the anterior wall of the uterus. This is in the outer layer. It reaches the surface and has become densely adherent to the bladder. There is a widespread diffuse adenomyoma of the posterior uterine wall, confined in large measure to the outer layers of the uterus. The pedunculated adenomyoma of the posterior

wall springs from this diffuse adenomyomatous area. The pedicle of the adenomyoma, however, does not contain uterine glands.

This is one of the most widespread distributions of adenomyoma of the uterus that I have ever seen.

CASE 2.—*A subperitoneal, pedunculated adenomyoma springing from the posterior surface of the uterus, filling Douglas' culdesac, firmly adherent to the sigmoid and easily recognized on account of its bluish black cysts* (Figs. 5 and 6).

History.—Mrs. T. H., aged 42, came to see me, Nov. 8, 1920, complaining of pain on the right side of the lower abdomen. Her menses began at 14 and were always regular. The flow was moderate in amount. There had been some pain just before the period. She had had one miscarriage.

Fig. 3.—Uterine mucosa in a pedunculated subperitoneal myoma (Gyn.-Path. No. 26352). This is an enlargement of the area *a* in Figure 2. A blood vessel just beneath the peritoneum is shown at *a*. Occupying the right and central portion of the field is a large island of uterine mucosa consisting of glands and stroma. Some of the glands are dilated. At *b* is a miniature uterine cavity.

Four years before I saw her, she fell from a chair, and two days later her period came on and lasted for twelve days. A little later she fell down thirteen steps, landing on her head. She had an attack of inflammatory rheumatism, and it was impossible for her to raise her hands.

Physical Examination.—She was well nourished and weighed 152 pounds. Her digestion had not been good.

I found the outlet moderately relaxed and the cervix small. Behind the cervix were two or three nodular lumps extending off to the right and there was a tumor mass which reached half way to the umbilicus and seemed to involve the body of the uterus. A diagnosis of multiple fibroids was made.

Operation.—The patient was admitted to the Church Home and Infirmary and operated upon, Nov. 11, 1920. When the abdomen was opened, we found the uterus retroposed and attached to the fundus a pedunculated myoma, 3 cm. in diameter. Just below this was the pedicle of a somewhat globular tumor that filled the pelvis. This tumor was firmly adherent to the sigmoid flexure and was loosened with a good deal of difficulty. As soon as we exposed it, we saw several bluish black cysts varying from 3 to 5 mm. in diameter just beneath the peritoneal surface of the tumor, and at one point an irregular oval area about 1 by 2 cm., with the characteristic brownish yellow color. It was perfectly clear that we were dealing with a pedunculated subperitoneal adenomyoma,

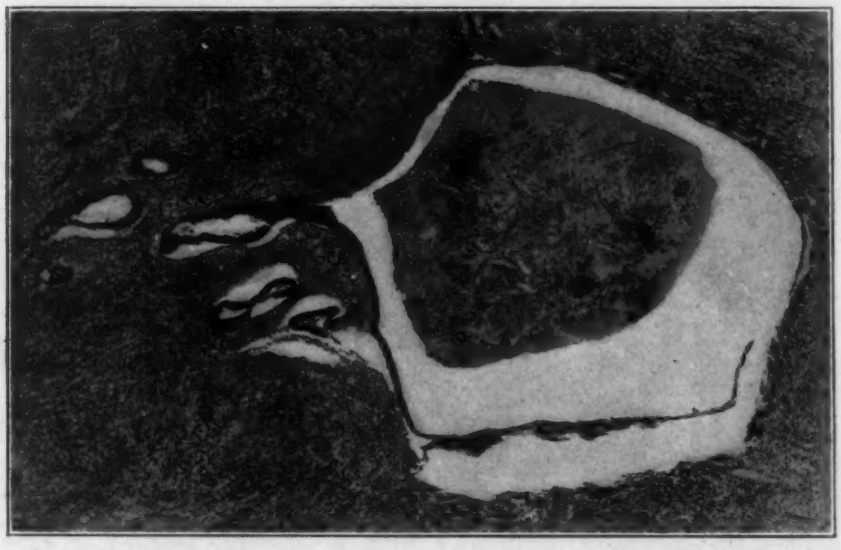

Fig. 4.—A miniature uterine cavity in a subperitoneal pedunculated adenomyoma (Gyn.-Path. 26352). This is an enlargement of the area *d* in Figure 2. Lining the cavity on the right is typical uterine mucosa. The remainder of the cavity is lined with one layer of more or less flattened epithelium, which for the most part lies in direct contact with the muscle. Partially filling the cavity are fragmented nuclei, polymorphonuclear leukocytes, old blood and crystals.

as a matter of fact, the best example of a pedunculated adenomyoma that I have ever seen. There was a little oozing in the pelvis near the right ureter, which was difficult to check. To remedy this we put in two cigaret drains and drew them out through the lower angle of the incision. The patient made an uninterrupted recovery.

Examination of Specimen (Gyn.-Path. No. 26354).—The specimen consists of a myomatous uterus. The uterus is 5.5 cm. in length, 6 cm. in breadth and 4 cm. in its anteroposterior diameter. It is only very slightly enlarged. Spring-

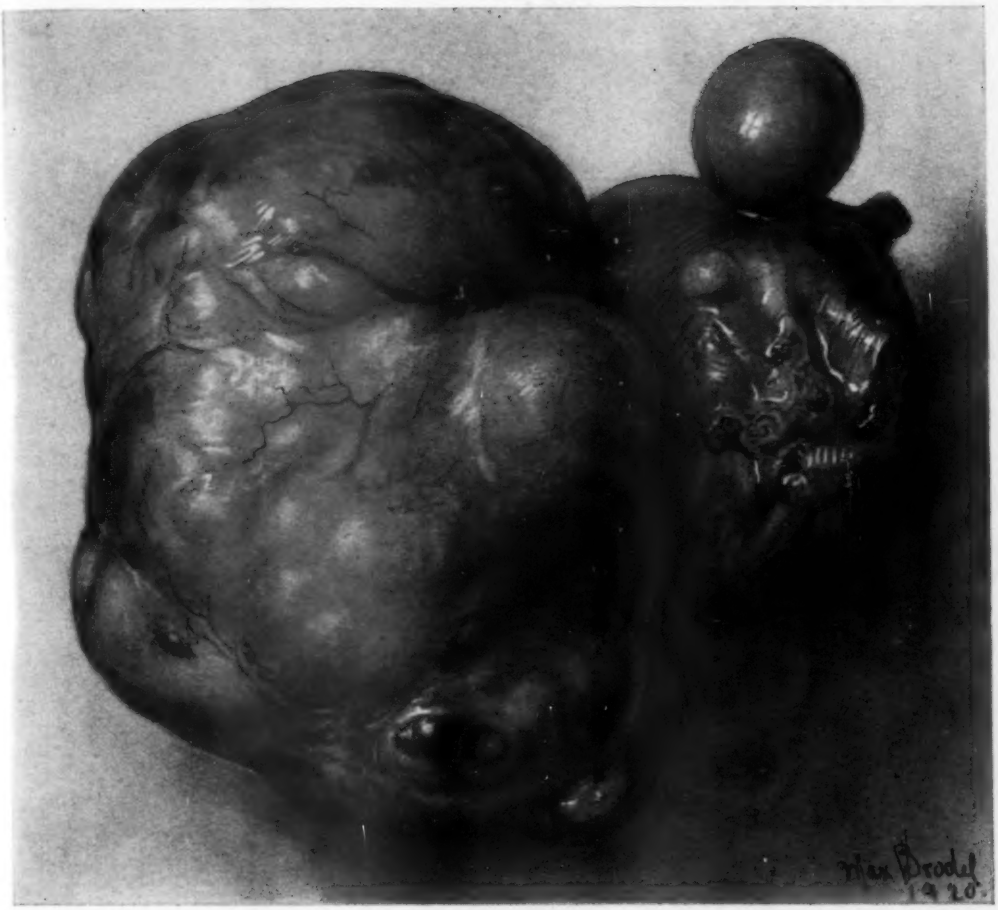

Fig. 5 (Case 2).—A pedunculated subperitoneal adenomyoma springing from the posterior surface of the uterus (Gyn.-Path. No. 26354). Attached to the surface of the uterus are a few small myomas. The chief interest centers in a lobulated pedunculated myoma springing from the posterior surface of the uterus. This tumor was firmly fixed at the floor of the pelvis and was intimately attached to the sigmoid. At the lower end of this tumor is a slightly yellowish area. This is where the pelvic fat was blended with the tumor. Shining through the peritoneum of the tumor are bluish black cysts and along the convexity near the middle is a rusty brown area. From the picture it is at once evident that we are dealing with a pedunculated subperitoneal adenomyoma. Figure 6 shows the appearance of this tumor on section.

UNIVERSITY OF MICHIGAN

Fig. 6.—A longitudinal section of a pedunculated subperitoneal adenomyoma of the uterus (Gyn.-Path. No. 26354). This is a longitudinal section of the subperitoneal pedunculated tumor seen in Figure 5. In the upper part of the specimen is a definite cavity with the muscle arranged spherically around it. In the middle of the convex surface, we find cross sections of several cysts which were filled with chocolate-colored contents. One of these cystic areas reaches the surface and corresponds to the situation of the rusty area noted in the water color. These cysts were lined with one layer of cylindric epithelium. In the lower part of the specimen are numerous small spaces. The majority of these are miniature uterine cavities. The picture is characteristic of a widespread adenomyoma on section.

ing from its surface are a few small myomas, varying from 1 to 7 mm. in diameter, and projecting from the top of the uterus is a pedunculated myoma, 1.5 cm. in diameter.

Springing from the posterior surface of the uterus near its top is a subperitoneal, slightly pedunculated myoma. This pedicle was so short that when I went to lift the tumor up it tore away from the uterus leaving no appreciable pedicle but just a raw area, 1.5 cm. in diameter. This myoma is roughly kidney-shaped, 11 cm. in its longest diameter, 7 cm. broad and 6 cm. thick. At one point is a fatty adhesion, 1.5 cm. long. The general appearance, as noted at operation, is well shown in Figure 5. Scattered over the surface are cysts. Some of them are 1 cm. in length, most of them are bluish black. At one point near the middle of the convex surface of the tumor is a brownish area, 1.5 cm. in diameter.

The tumor, on section, presents the usual myomatous picture, but at many points there are chocolate-colored areas (Fig. 6). These are more noticeable near the convex surface of the tumor. The bluish black cysts are filled with blood or grayish brown material, evidently old blood, or with a brownish material. At one pole of the tumor is a somewhat punctiform area, 3 by 4 cm. The punctiform spaces are filled with old blood or with a grayish black material. Here and there are yellowish brown areas. Without further examination, we could unhesitatingly say that this subperitoneal nodule is an absolutely typical adenomyoma.

Histologic Examination.—Sections from the endometrium show that it is relatively normal. The mucosa itself presents the usual picture. At some points, however, it shows a definite tendency to extend into the underlying muscle.

The small myoma projecting from the fundus presents the usual picture.

Sections from the cystic area of the kidney-shaped pedunculated subperitoneal myoma show typical miniature uterine cavities lined usually on one side with one layer of cylindric epithelium, on the other with a zone of normal uterine mucosa. They are filled with blood. Occasionally an isolated gland is found in the myomatous tissue. The cysts filled with chocolate-colored contents are for the most part lined with one layer of cylindric epithelium. In some places, this epithelium rests directly on the muscle, at other points there is a small layer of intervening stroma. Opening into the cyst spaces, one finds here and there normal uterine glands.

This is a fine example of a widespread adenomyomatous condition of a subperitoneal, pedunculated myoma.

CASE 3.—*Multiple uterine myomas; diffuse adenomyoma of the anterior and posterior uterine walls* (Fig. 7); *pedunculated, subperitoneal adenomyoma springing from the posterior uterine wall and filling Douglas' culdesac* (Figs. 8 and 9).

History (Gyn. No. 26421).—O. M., aged 35, white, married, was admitted to the Johns Hopkins Hospital, Nov. 27, 1920, complaining of nervousness, soreness in the left lower abdomen and shooting pains in the legs, more marked on the left.

The family history was negative, and the previous history, apart from occasional intermenstrual bleeding during the last year, was without interest. She had had one full-term child and six or seven induced abortions at the second month.

In 1913, following an abortion, the patient began to have pain in the left lower abdomen. In 1917, this became more severe. The patient was run

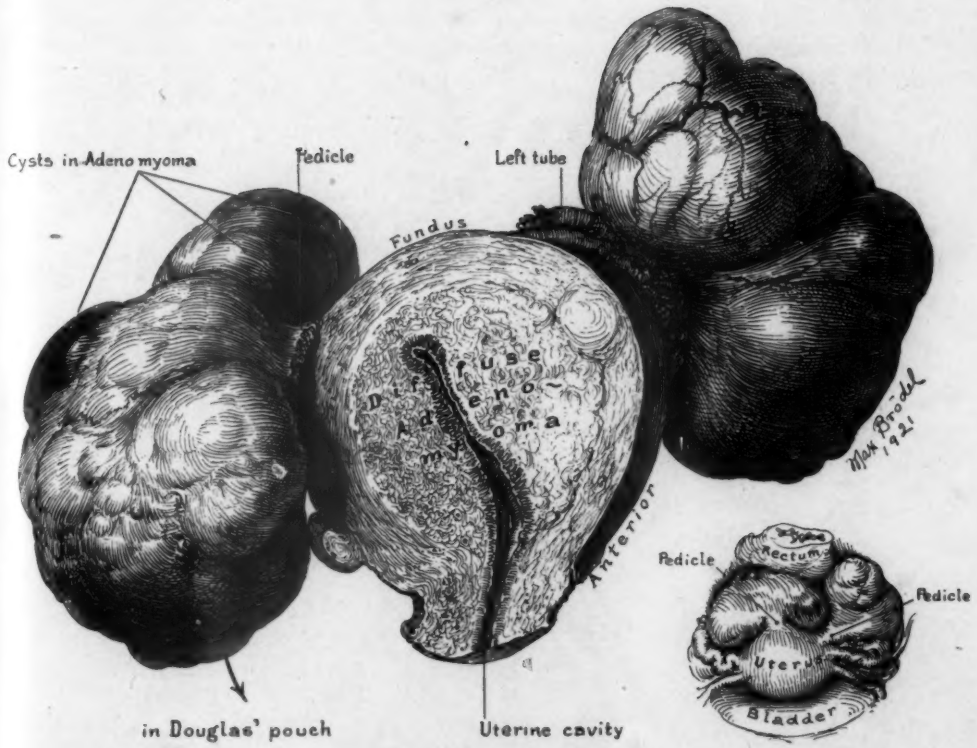

Fig. 7 (Case 3).—Subperitoneal, pedunculated adenomyoma associated with diffuse adenomyoma of both the anterior and posterior walls of the uterus (Gyn.-Path. No. 26401). The uterine walls are much thickened owing to the presence of a diffuse adenomyoma which occupies both the anterior and posterior walls. There are also a few small discrete myomas. Springing from the fundus just behind the insertion of the left tube is a lobulated myoma with numerous blood vessels coursing over its surface. Attached to the posterior surface of the uterus by a very short pedicle is a lobulated myoma which lay in Douglas' culdesac and was adherent to the sigmoid. Projecting from the surface of this were bluish black cysts. These are well shown in Figures 8 and 9. The relation of the uterus with its tumors to the bladder and rectum is indicated in a small sketch in the right lower corner.

down physically and was informed she had an abdominal tumor. From that time on the menstrual flow had been more profuse.

Physical Examination.—The Wassermann test was negative, the urine was normal, there were 9,600 leukocytes and hemoglobin was 65 per cent.

A firm, rounded tumor mass could be felt on the left side, extending 4 cm. above the symphysis. The outlet was moderately relaxed, the cervix was firm and pointed forward. In the posterior fornix was a hard nodular tumor, approximately 10 or 11 cm. in diameter. It appeared to be somewhat adherent. Movement of the cervix caused movement of both the anterior and posterior tumor masses.

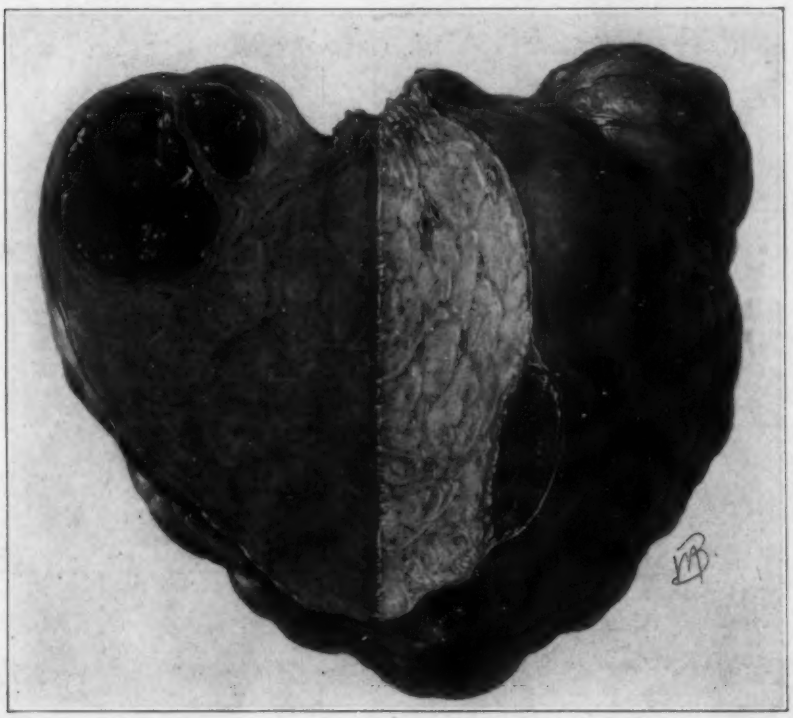

Fig. 9.—A subperitoneal pedunculated adenomyoma of the uterus (Gyn.-Path. No. 26401). The specimen has been so cut that about one fourth of it has been removed. We see the bluish black cysts noted in Figure 8, on section. They are filled with blood. The cysts were lined with one layer of cuboidal epithelium which in places was in direct contact with the myomatous muscle, at other points separated from it by a definite stroma. Scattered throughout the tumors were isolated glands lined with cylindric epithelium.

Operation.—Nov. 29, 1920, I removed the uterus, both tubes, the right ovary and the appendix. The hysterectomy was accomplished without much difficulty. The tumor occupying the culdesac tore away from the uterus and was removed separately. This tumor was somewhat adherent to the sigmoid. The bluish black cysts on its surface told us at once that we were dealing with a subperitoneal pedunculated adenomyoma. The left tube was apparently patent, though nodular. The right tube was the seat of a hydrosalpinx. The right

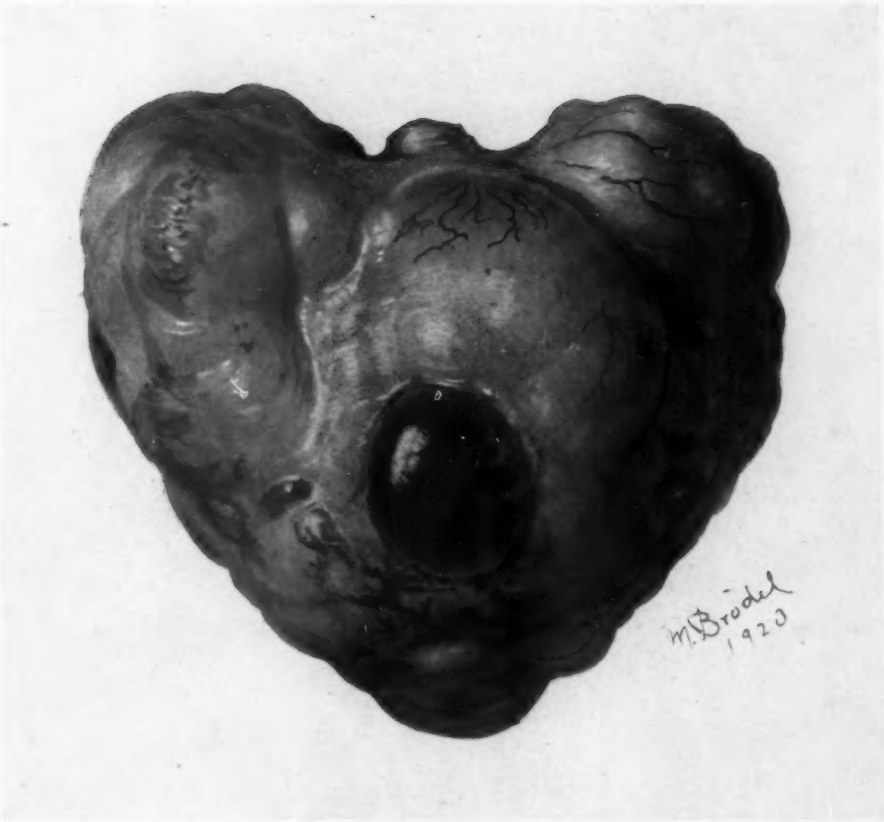

Fig. 8.—A pedunculated, subperitoneal adenomyoma of the uterus (Gyn.-Path. No. 26401). This is the pedunculated myoma which sprang from the posterior surface of the uterus seen in Figure 7. The tumor is lobulated, and projecting from its surface is a bluish black cyst. That there are other cysts similar in character is clearly evident from the bluish black appearance in the left upper portion of the picture. Several other small bluish black cysts are also noticeable along the left half of the specimen. The appearance of the specimen on section is shown in Figure 9. The gross appearance at once indicates adenomyoma. The tumor at operation was adherent to the sigmoid flexure.

ovary contained a corpus luteum cyst, 4.5 cm. in diameter. The postoperative course was uneventful and the patient was discharged Dec. 18, 1920.

Examination of Specimen (Gyn.-Path. No. 26401).—The specimen consists of a multinodular myomatous uterus which has been amputated through the cervix. Both tubes and the right ovary are also attached.

The uterus itself is 8 cm. long, 7 cm. broad and 6 cm. in its anteroposterior diameter. The anterior surface is relatively smooth, the posterior is covered with shaggy adhesions. The uterus on section shows a normal looking cavity. The posterior wall of the uterus reaches a thickness of 2.5 cm.; the anterior wall is 3.5 cm. thick. Forming a mantle around the upper two thirds of the uterine cavity and implicating both the anterior and posterior walls is a definite diffuse myomatous thickening, which immediately suggests adenomyoma (Fig. 7). Scattered throughout both the anterior and posterior walls are a few small discrete myomas varying from 8 mm. to 1.5 cm. in diameter.

Springing from the posterior surface of the uterus just behind the insertion of the left tube is a lobulated myoma, 10 by 7 by 6 cm., which shows large blood vessels coursing over its surface. On section it presents the usual myomatous picture.

Attached to the posterior surface of the fundus by a very short pedicle, 1.5 cm. in diameter, is a heart-shaped myoma, 9 by 7 by 6 cm. Near its convex surface, this shows a bluish black cyst, about 2.5 cm. long by 2 cm. broad. This is very well shown in Figures 8 and 9. Near the base of the tumor is a rather puckered area just to one side of the pedicle. The underlying tissue here looks rather bluish black. A few other smaller cysts are also noticeable. The bluish black cyst near the apex of the tumor has thin walls and contains blood (Fig. 9). The bluish black area near the pedicle shows a thin-walled cyst, 2.5 cm. in diameter, filled with dirty chocolate-colored material—old blood. This myoma on section, apart from the few cysts mentioned, presents the ordinary myomatous picture.

As was noted in the operative report, the left tube was nodular but patent. The right tube was the seat of a hydrosalpinx.

Histologic Examination.—Sections from the uterine wall show a widespread adenomyoma of the anterior wall, and a moderate grade of adenomyoma of the posterior wall. The uterine mucosa looks normal, as does also that scattered throughout the walls of the uterus. It is readily possible to trace the uterine mucosa directly into the underlying muscle.

Sections from the pedunculated myoma which sprang from the surface of the uterus just behind the insertion of the left tube show a good deal of hyaline transformation and some liquefaction. They do not show any glands.

Sections from the pedunculated nodule which sprang from the posterior surface of the fundus, and in which the bluish black cysts were seen, show that these cysts are filled with blood and that they are lined with one layer of cuboidal epithelium. This in some places is gathered up into little knobs. The epithelium sometimes rests directly on the muscle, sometimes it is separated from it by a definite stroma. Scattered throughout the myomatous tissue are a few small glands lined wih cylindric epithelium. There is no doubt that we have here an adenomyoma and that the blood in the cysts was of menstrual origin. The epithelial elements, however, in this myoma were very meager.

The association of the diffuse adenomyoma of both the anterior and posterior walls of the uterus and of the subperitoneal adenomyoma are very interesting. With such a combination as this the probable origin of the pedunculated subperitoneal adenomyoma is not difficult to surmise.

COMMENT

From a study of these three cases it is perfectly clear that a diagnosis of subperitoneal, pedunculated adenomyoma of the uterus is impossible unless, perchance, a submucous adenomyoma has been previously expelled, and even then a subperitoneal nodule might be only a simple myoma.

In Case 2 we found extension of the uterine mucosa into the muscle and in Cases 1 and 3 there was a diffuse adenomyoma of the uterine wall.

From these cases we can clearly see what complications may develop if such pedunculated subperitoneal adenomyomas are let alone. In previous cases we have found very small subperitoneal adenomyomas projecting from the uterine wall. In a few cases we have noted adenomyomas so intimately blended with the pelvic structures that their removal was utterly impossible.

In Case 1 the adenomyomatous elements of the pedunculated myoma had not yet reached the peritoneal surface of the tumor, but in Cases 2 and 3 the tumor had already become adherent to the sigmoid, the adhesion being particularly pronounced in Case 2.

The more we study adenomyomas the more fully are we convinced that they should, if possible, be removed as soon as they have been diagnosed.

I wish to express my heartiest thanks to Mr. Max Brödel, Director of the Department of Art in Medicine in The Johns Hopkins Medical School, for his remarkable illustrations and to Mr. Hermann Schapiro for his splendid photomicrographs.

OBSERVATIONS ON THE NORMALLY DEVELOPING ELBOW

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This study was prompted by a desire to know more about the appearance of the developing elbow. Certain facts stand out in bold relief to those who interest themselves in injuries about the elbow, or any other joint, in the young. Some of the points to be mentioned are self-evident, and yet a survey of the literature, or the comparative absence of such a literature, makes their mention of value.

This is only one of a series of studies which will be carried out in a like manner on other joints.

In order to study the subject in a systematic manner, I have divided the paper into four parts:

I. A review of the literature.

II. Observations on a series of normal elbows at various ages.

III. Descriptive findings of the individual roentgenograms.

IV. Clinical experience in the treatment of injuries of the elbow.

I. A REVIEW OF THE LITERATURE

The elbow in the young is frequently the seat of injury. Our predecessors were not so fortunate as we in having the valuable assistance of roentgenograms. In spite of this handicap, a review of the expressions of some of the authorities who wrote before the advent of the roentgen ray will demonstrate how well they utilized their minute knowledge of anatomy for the benefit of the patient. A similar review of more recent literature will prove that since the advent of the roentgen ray proper use has not been made of this aid.

It may prove of interest to others as it has to me to quote some of the authors of the modern period preceding the introduction of the roentgen ray.

Wheelhouse,[1] in 1885, wrote: "You should never consider your knowledge of the bones to be perfect until you have made the anatomy of the epiphyses as thorough as that of every other point in connection with them."

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1. Wheelhouse: Clinical Lecture, Surgery of the Epiphysis, Brit. M. J. 1:475, 1885.

Professor Smith said, "When the surgeon is called upon for his opinion respecting the nature of the injuries occurring in the vicinity of the larger joints in early life, he will find that the knowledge of the anatomy of the epiphyses is of the greatest importance."

Jonathan Hutchinson [2] writing in 1885 on injuries to the epiphyses stated:

"They constitute really a comparatively new topic, and it is almost astonishing to know that within the last half century the opinion was expressed strongly that separations of the epiphyses were impossible. Subsequently Delpeche, and again Malgaigne a few years later, stated as their opinion *that such* separations did not differ in any particular respect from fractures, and that there was no importance in attempting to distinguish between them.

"I am not far wrong in saying that in our current manuals on surgery of the day you will find comparatively little information with reference to these injuries.

"They are tolerably common. . . . They are important to recognize and treat." [3]

John Poland [4] in 1897, under the title of "Diagnosis of Traumatic Separation of the Epiphyses," was content to state that "these injuries can only occur, as a rule, in patients below 21 or 23 years of age before the epiphyses have become united by bone to the shaft."

A. H. Tubby,[5] in 1899, writing on "Traumatic Separation of the Epiphyses of the Upper Extremity" states: "The subject of traumatic separation of the epiphyses is now receiving a fuller measure of attention than formerly. Separations of the epiphyses are even more important than fractures, from their occurrence in young life and the important effects that may ensue in regard to the subsequent growth of the bone."

Case reports and museum specimens of epiphyseal separations are included in this paper, but no allusion is made to the ages at which various epiphyses appear, nor to ages of ossification, and no mention is made of the appearance of these lines and the possibility of misinterpreting them as fractures.

"It is indeed strange that so little has been written upon the subject of epiphyseal separation of the ends of the humerus, either by remote or modern surgeons, *but the epiphyseal structures are small and we are*

2. Hutchinson, J.: Injuries to the Epiphyses, Med. Press & Circ. **40**:461, 1885.

3. No mention is made of ages at which ossification occurs.

4. Poland, John: Diagnosis of Traumatic Separation of the Epiphysis, Pediatrics **4**:49-60, 1897.

5. Tubby, A. H.: Guy's Hosp. Rep. **31**:267-307, 1889.

Fig. 1.—Age, 17 months.

Fig. 2.—Age, 5 years.

Fig. 3.—Age, 5 years.

Fig. 4.—Age, 5 years.

ever conscious of the fact that nowadays most surgeons are looking for larger game," said Lucid [6] in 1899.

He added: "Ossification begins in the radial portion of the articular surface at the end of the second year; in the trochlear portion at the twelfth year, the internal condyle at the fifth year, and the external epicondyle at the fourteenth year. At the sixteenth and seventeenth years of life all of the centers are joined to each other and to the shaft, except the inner epicondyle, which does not unite with the shaft until the eighteenth year."

Fowler,[7] writing on the "Separation of the Epiphysis of the Lower Extremity of the Humerus," in 1899, under the heading of anatomy said: "The lower epiphysis of the humerus includes both epicondyles, the epiphyseal line being fairly straight and crossing the bone just above the two epicondyles. Directly over it lies the olecranon fossa. *The epiphysis has, at first, five separate centers of ossification.* These are subsequently reduced to three. The *ossification* in the *capitellum* is *said* to begin *during the third year."*

Hutchinson has found it at eighteen months and Farabeuf [8] says that "it usually occurs during the second year." The width of the epiphyses increases during the first few years. The depth increases slightly. The nucleus over the internal epicondyle appears at the fifth year. The third nucleus over the trochlear appears in the eleventh or twelfth year. A small separate nucleus appears over the external epicondyle. Fusion with the shaft is completed in the sixteenth or seventeenth year."

The epiphysis grows relatively smaller as the individual advances in years.

Modern anatomies and textbooks on surgery in general pay scant attention to this subject, as will be noted from the following:

The lower end of the humerus develops in the following manner: At the end of the second year ossification commences in the radial portion of the articular surface (capitellum) and from this point extends inward, so as to form the chief part of the articular end of the bone. The center for the inner part of the articular surface does not appear until about the age of 12. Ossification commences in the internal condyle at about the fifth year and in the external one not until the thirteenth or fourteenth year. At about 16 or 17 years, the

6. Lucid: Epiphyseal Separations of the Ends of the Humerus, New York M. J. **70**:406-409, 1899.

7. Fowler, R. S.: Brooklyn M. J. **13**:209 (April) 1899.

8. Farabeuf: Sur l'epiphyse inférieure de l'humérus et son décollement traumatique, Bull. et mém. Soc. de chir. de Par. **12**:692, 1886.

Fig. 5.—Age, 5 years.

Fig. 6.—Age, 6 years.

Fig. 7.—Age, 6 years.

Fig. 8.—Age, 6 years.

external condyle and both portions of the articular surfaces having already joined, unite with the shaft. At the eighteenth year the internal condyle becomes joined to the shaft.

The centers in the lower end of the humerus appear thus according to various authors: in the radial portion of the articular surface (capitellum), at the end of the second year (Knox); end of the second and third year (Cunningham); end of the second year (Gray): center for mesial half of trochlear at the twelfth year (Knox); eleventh to twelfth year (Cunningham); twelfth year (Gray). Internal condyle: fifth year (Knox); fifth year (Cunningham); fifth year (Gray). External condyle: thirteenth or fourteenth year (Knox); twelfth year (Cunningham); thirteenth to sixteenth year (Gray).

The external condyle and both articular surfaces unite between the sixteenth and seventeenth year (Gray); sixteenth and seventeenth (Cunningham); sixteenth and seventeenth year (Knox).

TABLE 1.—TIME OF APPEARANCE OF CENTERS IN THE LOWER END OF THE HUMERUS, ACCORDING TO VARIOUS AUTHORS

Author	Capitellum	Internal Epicondyle	Trochlea	External Epicondyle	Complete Ossification
Lucid (1899)	End of 2d year	5th	12th	14th year	16th to 17th year
Gray	End of 2d year	5th	12th	13th to 16th	
Knox	End of 2d year	5th	11th to 12th	13th	15th
Cunningham	End of 2d year	....	12th	12th	16th to 17th
Cotton	1½ years	5th	....	12th to 14th years	
Scudder	Generalities	Only	....	....	17th
Roberts and Kelly	1st year	10th to 12th	10th to 12th	10th to 12th	20th to 22d
Stimson	1st and 2d	....	Generalities		
Ashhurst	1st ½ year	6th year	11th	12th not constant	15 years

The internal condyle unites with the epiphysis at about the eighteenth year (Knox); from the eighteenth to the nineteenth year (Cunningham); eighteenth year (Gray). The epiphysis unites with the shaft about the fifteenth year or before the outer condyle unites with the articular surfaces (Knox); from the sixteenth to the seventeenth year (Cunningham); about the fifteenth year, or the same as Knox.

Cotton, writing on joint fractures and dislocations in 1910 under the title, "Anatomy of the Epiphysis" states: "At birth, and up to 2 or 3 years of age, the whole lower end of the humerus is a cartilaginous mass in which an ossification center appears at the outer side at about one and a half years of age.

"By 4 or 5 years of age the external condyle has become a definite structure and a cleavage line occurs in the cartilage that has been formed. The internal epicondyle shows a bone center at about 5 years and at

Fig. 9.—Age, 7 years.

Fig. 10.—Age, 8 years.

Fig. 11.—Age, 8 years.

Fig. 12.—Age, 9 years.

about 10 or 12 years it has been separated from the rest of the epiphysis by growth of the shaft downward into the epiphysis, leaving only a shell of epiphysis over the trochlear surface, with a small ossification center. From this time onward, growth occurs by progressive ossification of the external condyle and by growth of the diaphysis downward.

"The external condyle unites to the shaft usually between 16 and 19 years of age, but may persist longer.

"There is an ossification center of the external epicondyle appearing at 12 to 14 years fusing, as a rule, with the external condyle by the sixteenth year. This is never more than a scale and is surgically unimportant.

"Growth of the trochlear is by growth of the shaft down into the epiphysis, and the lower end of the ossified shaft becomes very oblique as time goes on.

"The last epiphysis to unite is that of the internal epicondyle. It may join as early as the sixteenth to eighteenth year, but often there is delay, and according to Ramband and Renault it may remain as an epiphysis through life."

Scudder says: "The lower epiphysis of the humerus unites to the shaft about the seventeenth year. The lower epiphysis of the humerus is made up of the external epicondyle, the capitellum and trochlear. These separate centers of ossification unite about the thirteenth year, and about the seventeenth year they join the shaft of the bone. The internal epicondyle is entirely separate from the large, general, lower humeral epiphysis."

Roberts and Kelly say: "The humerus is developed from a center of ossification for the diaphysis, which appears during the eighth week of fetal life, and six or seven secondary centers for the extremities which appear after birth, the epiphysis being cartilaginous. During the first year, the capitellum (of the lower extremity) appears. The trochlea, external and internal epicondyles appear between the tenth and twelfth years. Complete ossification and disappearance of the synchondrosis from the twentieth to twenty-second year."

Stimson says: "During the first or second year a center of ossification appears in the capitellum. Between the eighth and twelfth year this nodule enlarges, nearly or quite reaching the trochlear groove, a nodule appearing in each epicondyle, and the diaphysis sends a prolongation down into the inner portion of the trochlea.

"Between the twelfth and fifteenth years the nodule of the capitellum unites with that of its epicondyle, and after that the final point of ossification with that of the trochlea appears.

"The trochlea unites with the capitellum about the fifteenth year. Soon after there is union with the shaft."

Fig. 13.—Age, 9 years.

Fig. 14.—Age, 9 years.

Fig. 15.—Age, 10 years.

Fig. 16.—Age, 10 years.

Ashhurst [9] states: "The epiphyseal centers around the elbow appear in the following order: (1) capitellum of humerus in the first half year of life; (2) head of radius during the sixth year; (3) epitrochlea, or internal epicondyle, about sixth year of life; (4) trochlea during the eleventh year; (5) olecranon later in the eleventh year, and (6) epicondyle in the twelfth year. This center frequently cannot be detected.

II. OBSERVATIONS

It is manifestly impossible to interpret roentgenograms of joints in the young unless we have a standard for comparison. In the Surgeon-General's Index Catalogue, there is not a single work in English on the development of the epiphyses.

Many have probably made the same errors as we have, interpreting as fracture lines, and epiphyseal separations, normally developing epiphyses.

It might be said, and probably wisely, that such an error could not have crept in if the normal joint had been taken for the purpose of comparison. Such a procedure is advisable and necessary if no standard for comparison is available.

With a view to obtaining roentgenographic information relative to the developing elbow, we have had a series of roentgenograms of normal elbows taken. The ages of the subjects ranged from 6 months to 18 years.

The information obtained from the reading of these roentgenograms forms the basis of this paper.

Since the epiphyses develop through cartilage and since cartilage does not leave a shadow on the roentgenogram, the epiphyses are not apparent roentgenographically until some ossification has taken place.

The lower end of the humerus develops through four centers, one for the capitellum, for the internal epicondyle, the trochlear and the external epicondyle. The time of appearance of these epiphyses roentgenographically varies. The factors which influence this are probably environment, diet, and state of health. This problem is to be worked up at a later date.

The first epiphysis to appear roentgenographically is the capitellum The earliest record of its appearance is at 17 months. Up to the age of 5 years the capitellum is the only epiphysis which is evident roentgenographically. At some time during the fifth year the epiphysis in the head of the radius may appear. This is not constant, as during the sixth year of life the shadow for this epiphysis is often absent. During the seventh year, the epiphysis for the head of the radius is constantly found.

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9. Ashhurst, A. P. C.: Fractures of the Elbow, Philadelphia, Lea and Febiger, p. 30.

Fig. 17.—Age, 11 years.

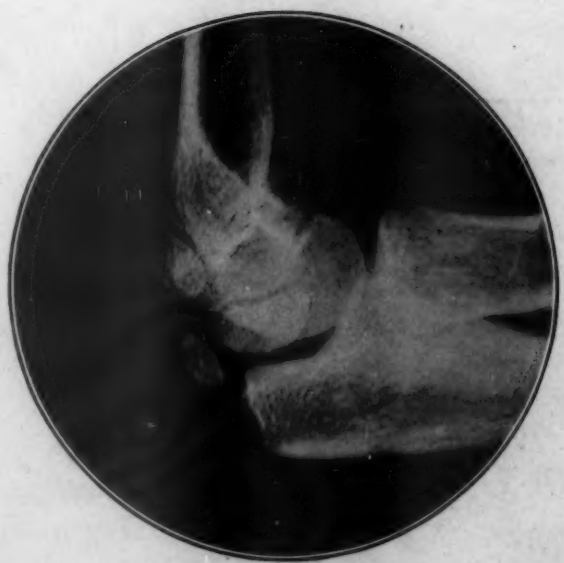

Fig. 18.—Age, 11 years.

Fig. 19.—Age, 11 years.

Fig. 20.—Age, 11 years.

The internal epicondyle appears in some instances at this age, but it is not constant. Here we notice a marked contrast between our findings and the statements in several well known textbooks. Reference to the portion of the paper in which we reviewed the literature will show that the time of appearance of the internal epicondyle is given as 5 years of age. We have not found it prior to 7 years of age. It is a curious fact that so many authors have accepted and apparently incorporated the errors of others in their own writings. Not *only is the internal epicondyle not constantly found at 7, when we first find it, but it is not always evident during the eighth, ninth, and tenth years.*

An appreciation of the relationship of the internal epicondyle to the shaft will be helpful in making the diagnosis of epiphyseal separation. The internal epicondyle appears close to, and almost continuous with, the internal oblique line of the shaft of the humerus: as the condyle develops it increases in size from above downward (Figs. 10 and 12).

TABLE 2.—Time of Appearance of Centers of Ossification in Epiphyses of Lower End of Humerus According to These Observations

Age	Capitellum	Internal Epicondyle	Trochlea	External Epicondyle	Ossification	Head of Radius	Olecranon
6 years	17 months 5 years Yes	0	0	0	0	½ circumference	0
7 years	Yes	20125-20121 Yes	0	0	0	Yes	0
8 years	Yes	Yes (not constant)	Yes (not constant)	0	0	Yes	Yes (not constant)
9 years	Yes	Yes (not constant)	Yes (not constant)	0	0	Yes	Yes
10 years	....	Yes (not constant)	Yes (not constant)	0	0	....	Yes
11½ years	Yes*	Yes	Yes	0	0	Yes	Yes
12 years	Yes*	Yes	Yes	0	Yes in one instance	Yes	Yes

* United with trochlea in some instances.

At 8 years of age we have noted a beginning olecranon and trochlea. These epiphyses are not constant at this time. Textbooks (Gray, Knox, Cunningham, Roberts and Kelly, Scudder and Ashhurst) give the time of appearance of the trochlea as the tenth to twelfth year. Reference to Figures 10, 11 (8 years) and 12 (9 years) demonstrates the early shadows of an ossifying trochlea. During the tenth year the trochlea develops to a considerable extent (Figs. 15 and 16). We are therefore forced to conclude that the trochlea does appear as early as the eighth year and is constantly found by the tenth year except in cases of underdevelopment.

The capitellum which is the first to appear develops from within outward, and by the tenth year occupies the base of the shaft of the humerus from the middle of the olecranon fossa outward.

Fig. 21.—Age, 11½ years.

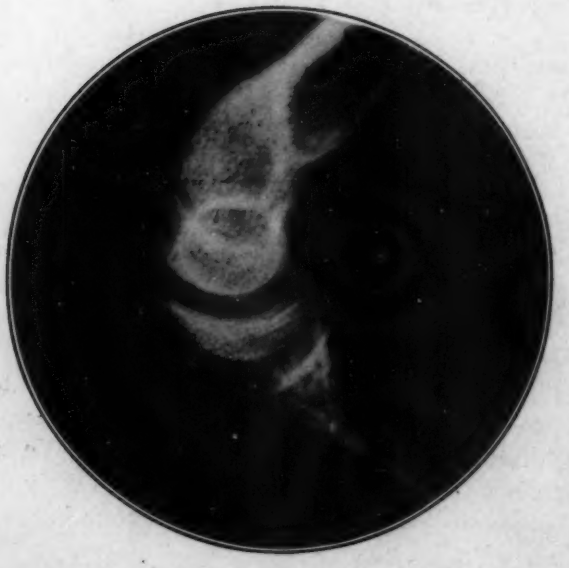

Fig. 22.—Age, 12 years.

Fig. 23.—Age, 12 years.

Fig. 24.—Age, 12 years.

During the eleventh year of life we have noted frequently a union between the capitellum and the trochlea, but no ossification of the epiphyses and the diaphysis. This is not, however, a constant finding, as we find the trochlea and capitellum still ununited in some instances at 12 and 13 years.

During the twelfth year of life the capitellum and trochlear have, in some instances, not only completely developed, but the epiphyseal line between them has become obliterated.

The olecranon and trochlea are the most variable epiphyses at this age. The trochlea is represented in some persons by a small shadow; in others, it has, as previously stated, become united to the shaft.

The olecranon epiphysis appears as early as the eighth year, in some instances as a small elliptical mass widely separated from the ulna. This finding is rare. Occasionally this epiphysis is manifest at 9 years.

During the tenth year, there are at times two distinct shadows in the region of the olecranon epiphysis. By this time this epiphysis is constantly found.

The two shadows for the developing olecranon suggest either an irregular ossification within one epiphysis, or two separate epiphyses, one for the tip and one for the posterior portion of the olecranon. The olecranon is constantly evident and well developed during the eleventh and twelfth years.

At this time, there is some union between the epiphysis and the shaft; the ossification between the two takes place from before backward.

The thirteenth year finds the capitellum and trochlea in most instances completely developed and united; but there is a line separating the united epiphyses from the diaphysis. In some instances, this union has occurred.

The internal epicondyle has not united to the shaft at 13; but the olecranon has become united by one-half its length to the shaft of the ulna.

The well developed head of the radius is also still separated by a line from its shaft. At 14 years of age, we find complete development and union of the epiphyses to their respective shafts, except the internal epicondyle. In one instance, we have noted that this has also occurred.

During the fifteenth, sixteenth and seventeenth years, this condition is noted, the internal condyle alone remaining ununited at 17 years.

Here again we note discrepancies in the literature. Various texts estimate the period of complete ossification as being from 15 to 22 years of age. One American textbook says ossification occurs between the period of 20 and 22 years. All of the texts refer to the external

Fig. 25.—Age, 12 years.

Fig. 26.—Age, 12 years.

Fig. 27.—Age, 12 years.

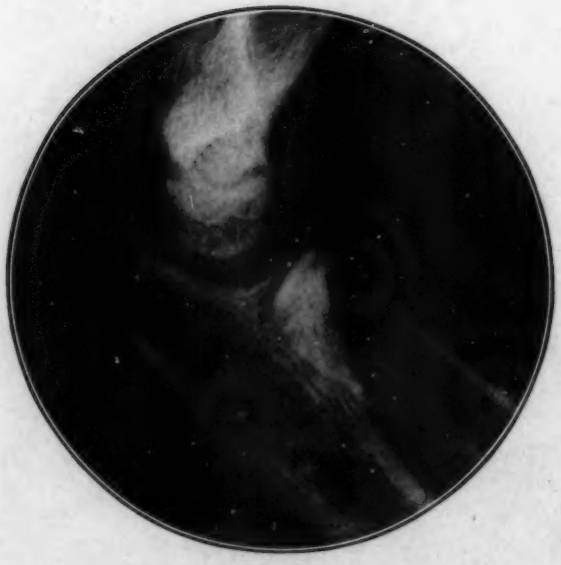

Fig. 28.—Age, 12 years.

epicondyle as appearing between the twelfth and sixteenth years. Our observations have led us to believe that it is not constant as a separate epiphysis. Its presence is the exception rather than the rule.

III. INTERPRETATION OF ROENTGENOGRAMS OF ELBOWS AT VARIOUS AGES

The first epiphysis to appear is the capitellum.

At Seventeen Months.—A small shadow is present below the shaft. The shadow is located in the plane of the anterior border of the shaft.

At Five Years.—The capitellum is still the only epiphysis which leaves a shadow. The position is slightly posterior to the plane of the anterior border of the shaft.

The plane of the axis of the capitellum intersects that of the shaft at an angle of approximately 60 degrees The anterior border of the capitellum is more closely approximated to the shaft than is the posterior border.

The capitellum roughly measures ½ cm. by ½ cm. (Figs. 2 and 3).

In Figures 4 and 5, the capitellum is nearly 1 cm. by ¾ cm. The epiphysis for the head of the radius is evident, occupying about one-half the circumference of the proximal end of the radius.

At Six Years.—In Figure 6, the capitellum alone is present (measuring not more than ½ cm. by ½ cm.), corresponding in development to that shown in Figures 2 and 3, of a 5 year old patient.

The capitellum (measuring 1½ by 1½ cm.) is closely approximated to the shaft. The head of the radius is one-half the size of the circumference of the shaft (Figs. 7 and 8).

At Seven Years.—The capitellum measures 1½ cm. by 1 cm. and is above the olecranon fossa (Fig. 9).

The internal epicondyle appears as a small round shadow below and internal to the shaft. The head of the radius is one-half the size of the circumference of the shaft.

At Eight Years.—These centers are present: the capitellum, internal epicondyle, trochlea, olecranon, and head of the radius.

The capitellum measures 1½ cm. by 1 cm. It extends outward, so that its external margin is practically continuous with the external oblique line of the broad lower end of the shaft of the humerus. The internal epicondyle is about ½ cm. by ¾ cm. and is separated by a rather marked clear space from the internal oblique line of the shaft of the humerus. The trochlea is represented by a tiny shadow internal to the capitellum and separated from it by about ½ cm. The olecranon is represented by a similar small shadow. The epiphysis of the head of the radius occupies about three fourths of the circumference of the upper end of the shaft of the radius (Fig. 10).

Fig. 29.—Age, 12 years.

Fig. 30.—Age, 13 years.

Fig. 31.—Age, 13 years.

Fig. 32.—Age, 13 years.

In Figure 11, the appearance is practically that of the preceding picture with the exception of the fact that there is no shadow for the olecranon.

In one instance, there was no shadow for the olecranon, nor for the trochlea. The capitellum has not extended so far out as in the previously described roentgenograms. There is no evidence of an internal epicondyle nor trochlear process. The diaphysis has extended downward, particularly on the inner side.

In another patient of the same age, there is no center for the olecranon nor trochlea. The lower end of the diaphysis of the humerus shows the same tendency to broaden out and extend downward on the inner aspect. There is no internal epicondyle.

At 8 years of age, we have in some instances only one epiphysis sufficiently ossified to manifest itself, that being the capitellum. The other extreme noted for the same age shows well developed capitellum, internal epicondyle, head of the radius, and small shadows of early ossifying trochlea and olecranon (Fig. 10).

At Nine Years.—In Figures 12 and 13, the internal epicondyle is present, the dimensions being ½ cm. by 1 cm. Its upper limit is practically on a level with the oblique line of the shaft. The capitellum measures 2 cm. by 1 cm. in its greatest long axes. Its growth is more marked to the radial side. The trochlea is represented by two shadows ¾ cm. by ½ cm. There is no evidence of an olecranon epiphysis. The epiphysis of the head of the radius occupies almost the entire circumference of the upper end of the shaft. The epiphysis for the head of the radius seems divided as though there were a loss in continuity. Probably this is indicative of an irregular ossification going on in this epiphysis. The capitellum extends fully ½ cm. anterior to the plane of the long axis of the shaft of the humerus.

At Nine Years.—In Figure 14, the internal epicondyle is present, the capitellum developing as in previous descriptions. The epiphysis of the olecranon is evident as a small elliptical shadow. The head of the radius is as usual. Two small shadows suggestive of beginning trochlear process are visible.

A shadow of the olecranon epiphysis is not present in some cases at 9 years, in others it has ossified sufficiently to leave a shadow ¼ cm. in diameter. The trochlea in some is not present, in others there are two shadows present, ¾ cm. by ½ cm.

At Ten Years.—There is no evidence of an internal epicondyle, no evidence of a trochlea, and no evidence of an olecranon in some cases at this age.

In others at 9 years, the capitellum is well developed, occupying that portion of the lower end of shaft from the middle of the olecranon fossa outward (Figs. 15 and 16). There is a distinct epiphysis for the external condyle. The trochlea has developed inward, but has not yet

Fig. 33.—Age, 13 years.

Fig. 34.—Age, 13 years.

Fig. 35.—Age, 13 years.

Fig. 36.—Age 13 years.

united with the capitellum. The internal epicondyle occupies the space between the trochlea. There is no union between the epiphyses and the shaft. The olecranon epiphysis is separated by a wide margin from the shaft of the ulna.

At Eleven Years.—Almost complete ossification of the capitellum and trochlea is shown in Figures 17 and 18.

Union has taken place between the two epiphyses; but they have not become united to the shaft. The internal epicondyle has not united to the shaft. There is no evidence of an external epicondyle.

There are two distinct shadows in the portion of the olecranon epiphysis, suggesting either two separate epiphyses or separate centers of ossification within one epiphysis. The head of the radius still presents the epiphyseal line of separation from the shaft. Figures 19 and 20 present a similar picture with the exception of a more marked development of the olecranon.

At Twelve Years.—Complete ossification and union of the capitellum and trochlea have taken place; a persistent epiphyseal line between the shaft and the united epiphyses may be noted (Figs. 22 and 23).

There is a persistent epiphyseal line between the internal epicondyle and the shaft. There is no evidence of an external epicondylar epiphysis. The olecranon is completely ossified, but persists in having an epiphyseal line. The head of the radius has not become united to the shaft.

Figures 24 and 25 differ from the preceding in that the olecranon is less well developed.

The internal epicondyle is about ¾ by ½ cm.; the capitellum and trochlea have united and occupy practically the entire lower aspect of the shaft. The head of the radius occupies the entire circumference of the upper end of the shaft. The olecranon seems to be made up of two portions, which are approximated from tip backward, more closely in front.

Varying Appearance at Twelve Years.—The olecranon shadow is absent in one (Fig. 27); a small shadow in one (¼ cm.), in another ¾ cm.; almost completely ossified in another. The ossification is more complete near the anterior portion of tip; there is still some separation posteriorly.

The capitellum continues to increase in size; and in some instances there is ossification to the trochlea and to the shaft.

The epiphyseal line is almost entirely obliterated in one instance (Fig. 29).

The trochlea shows a variable stage of development from a small shadow to a completely developed epiphysis, first becoming ossified to the capitellum and later to the shaft.

Fig. 37.—Age, 13 years.

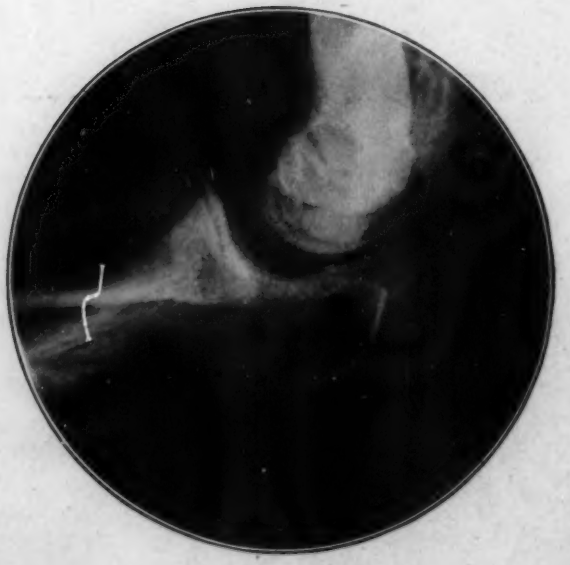

Fig. 38.—Age, 13 years.

Fig. 39.—Age, 14 years.

Fig. 40.—Age, 14 years.

The internal epicondyle is constantly present; in one instance, the epiphyseal line is completely obliterated (Fig. 26).

The capitellum (2½ by 1 cm.) extends from the middle of the olecranon fossa outward. The internal epicondyle is increasing in size.

The trochlea is represented by large nodules, not yet united to the capitellum.

There is no evidence of an external epicondyle, and no evidence of an olecranon. The head of the radius covers the entire circumference of the upper end of the shaft. Figure 28 corresponds almost entirely to Figure 27, except that the olecranon nodule is present, but small. There is no evidence of ossification of the epiphyseal centers to one another, nor union of centers to the shaft.

At Thirteen Years.—The capitellum extends from the middle olecranon fossa to the level of the outer border of the oblique line of the lower end of the humerus, 2½ by 1 cm. The epiphyseal line is still well marked (Fig. 30).

The trochlear nodule is larger than in previous years; but there is no union with the capitellum. There is still an epiphyseal line between the internal epicondyle and the shaft. The olecranon nodule is smaller than in some roentgenograms of previous years. The head of the radius occupies the entire upper end of the shaft of the radius; there is no union.

There is union of the trochlea and capitellum (Fig. 32). There is no evidence of the epiphyseal line between the shaft and the united capitellum and trochlea. The epiphyseal line between the internal epicondyle and the shaft is still present.

There is a shadow which is evidently developing upward from the capitellum in the direction of the external epicondyle, suggesting that the external epicondyle may be an outgrowth from the capitellum in some instances.

The olecranon epiphysis is almost completely ossified and is united for one half of its length to the ulna. Union is taking place from before backward.

Figure 33 is practically identical to Figure 32, except that the line between the shaft and the united lower epiphysis seems to have been obliterated.

In Figure 35, there is ossification and union of the capitellum and trochlea, but a persistent epiphyseal line separating the epiphyses and the shaft. The internal epicondyle persists in having an epiphyseal line separating it from the shaft.

The olecranon and head of the radius are still separate from their respective shafts.

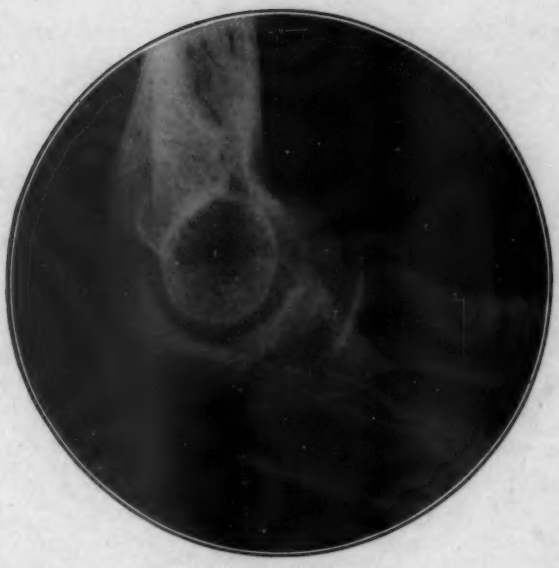

Fig. 41.—Age, 14 years.

Fig. 42.—Age, 14 years.

Fig. 43.—Age, 15 years.

Fig. 44.—Age, 15 years.

Figures 37 and 38 show distinctly less development of all of the epiphyses.

At Fourteen Years.—Figures 39 and 40 show complete ossification of all the epiphyses and union of all with the shaft except the internal epicondyle. Figure 41 is the same as Figures 39 and 40 except that there is union of the internal epicondyle to the shaft (Figs. 41 and 42).

At Fifteen Years.—There is complete ossification and union of the epiphyses with the shaft (Figs. 43 and 44).

Figures 45 and 46 show a persistence of all epiphyseal lines. There is a well marked epiphysis for the external epicondyle.

At Seventeen Years.—There is complete ossification and union of all the centers to the shaft (Figs. 47 and 48).

SUMMARY

1. The value of the proper knowledge of the roentgenographic appearance of the normally developing elbow can hardly be overestimated.

2. Many cases have been misinterpreted as fractures of one condyle or another, *which probably should have been interpreted as normal joints.*

3. Emphasis should be laid on the proper position for taking pictures of the developing joints. It seems that the anteroposterior view of the elbow in complete extension, with the forearm in complete supination, gives the best opportunity for observing the normal relationship of the developing epiphyses.

The literature on the subject gives misleading ideas of the time at which the epiphyses unite. Certainly there is no agreement among the authorities as to the period at which union occurs.

We have noted roentgenographically four centers of ossification for the epiphysis of the lower end of the humerus; the capitellum, internal epicondyle, trochlea, and occasionally the external epicondyle as a separate center. The first to appear is the capitellum; this is the only epiphysis present up to 5 years. The internal epicondyle appears next. It is important to note that the internal condyle appears close to and is continuous with the *internal oblique line of the shaft of the humerus.*

At the age of 14 years, we have found complete union of the epiphyses and the shaft with the exception of the internal epicondyle; this may remain ununited at 17 years of age.

The developing capitellum occupies a relatively constant position. This position can be determined best by passing a plane through the middle of the long axis of the shaft of the humerus.

Fig. 45.—Age, 15 years.

Fig. 46.—Age, 15 years.

Fig. 47.—Age, 17 years.

Fig. 48.—Age, 17 years.

This plane is intersected at an obtuse angle by a plane bisecting the developing capitellum (Figs. 4 and 5). The plane which bisects the shaft of the humerus is posterior to the posterior limit of the capitellum.

The diagnostic value of these intersecting lines will be fully detailed in a subsequent paper to be based on injuries about the elbow.[10]

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10. In addition to the references already given, the following will be found of interest:

Windle: United Epiphysis, Proc. Anat. Soc. Great Britain & Ireland, 1889.

MacDougall: A Note in Connection with Injuries to the Epiphysis, Edinburgh M. J. **36**:825-830, 1890-1891.

Draver, H. C.: Epiphyseal Separation of the Humerus, Univ. Mag. **9**: 118-203, 1896-1897.

Eccles: Traumatic Separations of the Lower Epiphysis of the Humerus with Displacement Forward, Lancet **2**:688, 1898.

Hamilton, F. H.: A Practical Treatise on Fractures and Dislocations, Philadelphia, 1890, p. 191.

THE HISTOGENESIS OF MALIGNANT TUMORS OF THE TESTICLE *

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Tumors of the testicle constitute one of the most confused and confusing subjects in the field of pathology. A wide variety of terms made their way into the earlier literature; these in turn became incorporated into complicated classifications in the textbooks on surgery. During more recent years, these tumors have formed the basis of a number of careful reports, through which the classification, based on histogenesis, should become simplified. Unfortunately, there is still some difference of opinion as to the origin of several testicular tumors which show undoubted histologic differences. Ewing,[1] in 1911, made a painstaking analysis of the previously reported cases, from which and from the study of nineteen cases of his own, he reached conclusions which, if they could be fully accepted, would greatly simplify matters. He believed that pure tumors of mesoblastic origin, such as fibroma, chondroma, myxoma, myoma and lipoma, are extremely rare and that most of such benign tumors have been derived from teratomas. What is of greater importance, he held that the malignant tumors are likewise teratomatous in origin and are the result of the onesided development and overgrowth of atypical epithelial tissue. Even if one is unwilling to accept in its entirety Ewing's view that all testicular tumors are teratomatous in origin, it is unfortunate that his article is not more widely known, because there would then be fewer reports of sarcoma of the testicle, undoubtedly one of the rarest of the tumors of this organ; and there would be less confusion and better mutual understanding when the surgeon, who thinks of sarcoma as the most frequent type of tumor, receives from the pathologist a diagnosis of carcinoma or embryonal carcinoma. Of Ewing's nineteen tumors, the last is termed an "example of genuine primary lymphosarcoma of the testis." No proof of the teratomatous origin is given except that the tumor arose in the rete, the point of origin of teratoma; perhaps the conclu-

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*From the Nelson Morris Memorial Institute for Medical Research and the Surgical Service of the Michael Reese Hospital.

1. Ewing, James: Teratoma Testis and Its Derivatives, Surg., Gynec. & Obst. **12**:230 (March) 1911.

sion reached from the study of the whole group, that all testis tumors originate in teratomas, has influenced the decision to include this tumor among those of teratomatous origin. Six are carcinomas with lymphoid stroma and without other heterologous elements.

In the literature since the appearance of Ewing's article there have been reports of sarcoma by Fata,[2] Stokes,[3] Codman and Sheldon,[4] Leuzzi,[5] Petit de la Villéon,[6] Smith,[7] Lister,[8] Grant,[9] Aguirre,[10] Fansler;[11] of perithelioma by Nizzi [12] and by Brandeis;[13] of hypernephroma by Thompson;[14] of fibroma by Lardennois and Lecène,[15] by Makins,[16] and by Boyer,[17] and of fibrolipoma by Baldwin.[18] In most of these, the microscopic description is too incomplete to permit critical study, but all are probably epithelial tumors except the fibromas and the fibrolipoma. The reported fibromas are apparently pure tumors derived from the tunic of the testis. The 23½ pound fibrolipoma reported by Baldwin was probably teratomatous in origin.

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2. Fata, M.: Considerazioni sopra un interessante caso di sarcoma del testicolo in un bambino di sei anni, Riv. di sc. med. **56**:547, 1912; ibid. **57**:14, 1912.

3. Stokes, A. C.: Sarcoma of the Testicle, with Report of a Case, New York M. J. **95**:438, 1912.

4. Codman, E. A., and Sheldon, R. F.: The Prognosis of Sarcoma of the Testicle, Boston M. & S. J. **170**:267, 1914.

5. Leuzzi, F.: Enorme sarcoma del testicolo destro, Gior. internaz. d. sc. med. **36**:693, 1914.

6. Petit de la Villéon, E.: Volumineux sarcome du testicule chez un enfant de vingt cinq mois, J. de méd. de Bordeaux **43**:781, 1913.

7. Smith, O. C.: Bilateral Sarcoma of Undescended Testes, Boston M. & S. J. **170**:839, 1914.

8. Lister, C. R.: A Case of Sarcoma of the Undescended Testis, M. J. Australia **1**:31, 1915.

9. Grant, W. W.: Sarcoma of the Intra-Abdominal Testis, J. A. M. A. **67**:915 (Sept. 23) 1916.

19. Aguirre, R. T.. Globocellular Sarcoma of the Right Testicle, Surg., Gynec. & Obst. **27**:47 (July) 1918.

11. Fansler, W. A.: An Unusually Large Sarcoma of the Testicle, Am. J. Surg. **32**:10 (Jan.) 1918.

12. Nizzi, U.: Sopra un peritelioma del testicolo in un lattante, Riv. di clin. pediat. **9**:652, 1911.

13. Brandeis, R.: Tumeur du testicle d'origine périvasculaire, Gaz. hebd. d. sc. méd. de Bordeaux, **35**:65, 1914.

14. Thompson, J. E.: Hypernephroma Arising in the Right Testicle, Tr. South. Surg. & Gynec. Assn. **23**:408, 1911.

15. Lardennois, G., and Lecène, P.: Fibrome de l'albuginée, Bull. et mém. Soc. anat. de Paris **86**:712, 1911.

16. Makins, G. H.: Multiple Fibromata of the Tunica Vaginalis, Proc. Roy. Soc. Med. **5**:155, 1911-1912.

17. Boyer, E. E. H.: Fibroma of the Testicle, Ann. Surg. **70**:210 (Aug.) 1919.

18. Baldwin, A.: A Case of Fibrolipoma of Testicle, Weighing Twenty-Three and a Half Pounds, West Lond. M. J. **22**:78, 1917.

Miyata [19] studied twenty-seven tumors, for which he gives the following diagnoses: twenty-one sarcomas; one sarcoma in a mixed tumor; one carcinoma; one perithelioma and three endotheliomas. Of his sarcomas, one was a fibrosarcoma of the tunic of the epididymis,

Fig. 1.—Cut surface of part of tumor from Case 1.

one a small spindle cell sarcoma of the sheath of the spermatic cord, and one a spindle cell sarcoma of the tunic of the testis. These three

19. Miyata, T.: Zur Kentniss der Hodengeschwülste und die Bedeutung des Traumas für ihre Entstehung, Arch. f. klin. Chir. **101**:426, 1913.

may perhaps be considered homologous pure tumors, although the descriptions are very brief. The rest are probably all epithelial tumors.

In a collection of fifty-nine tumors of the undescended testicle made by Bulkley,[20] the published diagnosis was sarcoma of one form or another in all except these: teratoma, 2; epithelioma, 2; chorio-epithelioma, 2; carcinoma, 7; rhabdomyoma, 1, and cancer, 5.

In addition to these, there have been a number of reports on cases of carcinoma, chorio-epithelioma, and malignant teratoma, which are more in accord with modern ideas. Among the latter articles are several more extensive studies by authors, most of whom do not accept Ewing's theory of the teratomatous origin of all testicular tumors, although they admit the carcinomatous nature of the tumors usually described as sarcomas.

The important literature previous to 1911 has been so well summarized by Ewing [1] that the reader is referred to his article. Frank,[21] in 1911, studied fourteen examples of the large cell, medullary tumor, which is the most frequent type of testicular tumor. The tumors are cellular, with little reticulum. The cells are large, with finely granular cytoplasm and large vesicular nuclei. Frank believes these cells are derived from the germinal cells of the tubuli contorti and asserts that all transition stages from the normal to the neoplastic cells are found. He agrees, therefore, with Birch-Hirschfeld, Tizzoni, Langhans, Chevassu and those others who maintain that the tumor which occurs most frequently is derived from normal, differentiated cellular elements of the testis and not from the constituents of a teratoma. He described also a vascular tumor of the angioplastic sarcoma type, composed of cuboidal, cylindric and irregular cells, and another tumor of mixed type with glandular alveoli, sarcoma-like tissue and smooth muscle. In the latter case, he excludes mixed tumor, for what reason it is not quite clear except that it may be from his desire to derive this tumor and the preceding one from the tubuli recti. He also described a fibro-adenoma, which he compared in structure with fibro-adenoma of the mamma. This involved both testis and epididymis, and Frank believes the tumor is derived from the latter structure. He admits that there are all gradations in histologic structure from the large cell tumor, which he considers a homologous pure tumor of tubular epithelium, to the heterologous mixed tumors. He does not accept the view of the origin of the latter from misplaced blastomeres, but derives them from unripe germinal cells, as opposed to the large cell tumor which is

20. Bulkley, Kenneth: Malignant Disease of the Testicle Retained Within the Abdominal Cavity, Surg., Gynec. & Obst. **17**:703, 1913.

21. Frank, A.: Die histogenetische Ableitung der Hodentumoren, Frankfurt. Ztschr. f. Path. **9**:206, 1911.

derived from ripe cells. This conception explains the varied cytomorphology, but is not susceptible of actual proof. He admits also the possibility of tumors being derived from interstitial cells. According to Frank, there can occur in the testicle four types of tumor: (1) carcinoma derived from differentiated germinal cells of the tubuli contorti; (2) carcinoma derived from the cells of the tubuli recti; (3) mixed tumors, often carcinomatous, from unripe germinal cells, and (4) sarcoma from interstitial cells.

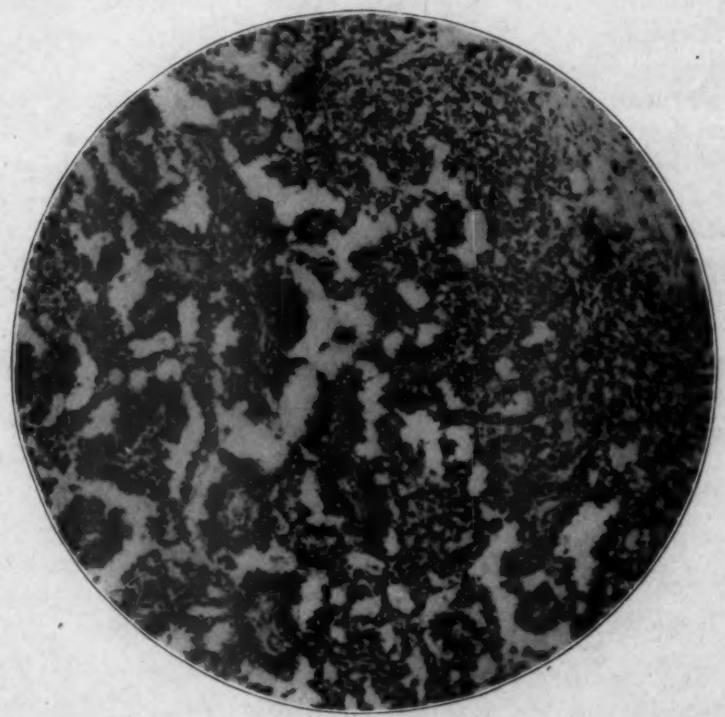

Fig. 2.—Atypical glandular and papillary tissue of tumor from Case 1. ×80.

Stoppato [22] in the same year (1911) concerned himself with tumors of supposed interstitial cell origin, of which Ewing [1] considers that only two examples have been reported, both being hyperplasias rather than neoplasms. Stoppato reports three cases. Whereas Frank holds that the heterogeneous group of alveolar sarcoma, endothelioma, angiosarcoma, etc., are really carcinomas of germinal cell origin, Stoppato concludes that most of the tumors of this group are interstitial cell tumors. The cells of his tumors he describes as being large, epithelial-like, loosely

22. Stoppato, U.: Ueber Zwischenzellentumoren des Hodens, Ziegler's Beitr. z. path. Anat. **50**:113, 1911.

arranged without intercellular substance, forming indistinct cords or solid cell masses. In one of his illustrations, the tumor has a distinctly alveolar character. There can be little doubt that Stoppato's interstitial cell tumors belong to the same group as Frank's germinal epithelial tumors, but derivation of the former from interstitial cells has not been rendered very probable.

Vecchi [23] (1912) studied more especially the mixed tumors of the testis, which he divides into three groups: (1) teratoma or embryoma of Wilms, organoid, usually cystic, relatively benign; (2) teratoid or embryoid tumors of Wilms, solid, often with small cysts, less completely differentiated than the first group. The relation of the structural elements to one another deviates to a greater degree from the normal than is the case in tumors of the first group; (3) mixed tumors derived from the mesoderm of the host, solid, no derivatives of ectoderm or entoderm, but mesoblastic and glandular derivatives of the mesoderm. Tumors of the last group are derived from totipotent cells of the mesoderm, i. e., from cells of the primitive urogenital anlage. They, therefore, are analogous to the congenital mixed tumors of the kidney. Tumors of the first two groups are derived from totipotent blastomeres, which have the value of ova. Of the twenty-four tumors studied, only three were considered teratomas, the rest mesoblastic mixed tumors. Vecchi admits that there are gradations, so that distinction between the three groups is not always possible. In addition to the mixed tumors, Vecchi accepts the derivation of tumors from tubular epithelium, interstitial cells, endothelium and supporting tissues.

Mori [24] (1912) studied a teratoma which contained derivatives of the three germ layers and which gave rise to chorio-epitheliomatous metastases. He concludes that the metastases are derived, not from totipotent cells, but from that element whose growth capacity has become developed to the greatest degree in the original tumor. Different teratomas, as compared with one another, may, therefore, give rise to different kinds of metastasizing tissue, but in any given tumor all the metastases will be formed by the particular tissue components of the primary tumor which have taken on malignant proliferation.

Sakaguchi's article [25] (1913) was based on the personal study of thirty-two cases, which he groups thus: one sarcoma; twenty-one typical large cell tumors; two atypical large cell tumors; seven epithelial

23. Vecchi, A.: Teratome, teratoide Geschwülste und Mischtumoren des Hodens, Deutsch. Ztschr. f. klin. Chir. **114**:104, 1912.

24. Mori, T.: Ueber ein metastasierendes Hodenteratom, Virchows Arch. f. path. Anat. **207**:99, 1912.

25. Sakaguchi, Y.: Zur Kenntnis der malignen Hodentumoren, vor allem der epithelialen, Deutsch. Ztschr. f. klin. Chir. **125**:294, 1913.

tumors with partly adenomatous and partly papillary proliferation, and one tumor with adenomatous areas and also solid cell nests. The sarcoma is diagnosed as a small spindle cell sarcoma. The description is meager, and it is impossible to decide whether this was a true pure sarcoma, a sarcoma derived from a mixed tumor, or perhaps an epiblastic epithelial tumor of teratomatous origin. Most interest attaches to the group of twenty-one typical and two atypical large cell tumors.

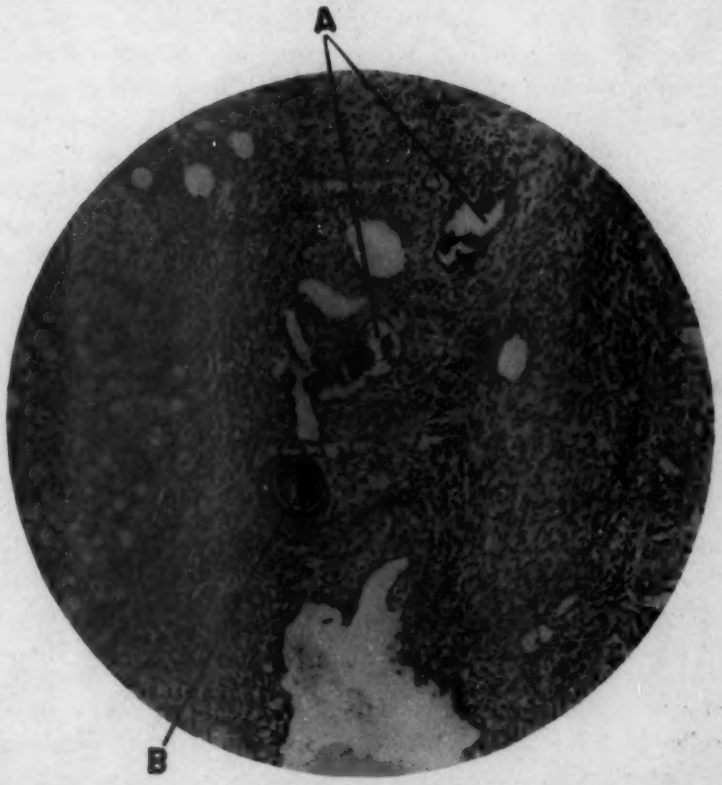

Fig. 3.—Differentiated heterologous tissue of tumor from Case 1: *A*, gland-like structures lined by cylindric epithelium; *B*, a mass of squamous epithelium. ×80.

These, as the author admits, undoubtedly belong to that most frequent type of tumor of the testis which has been the subject of so much study, the kind of tumor which formed the basis of the reports of Frank[21] and Stoppato.[22] In his review of the literature relating to this group, Sakaguchi thus summarizes the previously held views: (1) carcinoma, derived from (*a*) differentiated epithelium of convoluted tubules (Birch-Hirschfeld, Tizzoni, Langhans, Chevassu, Frank); (*b*) embryonic tubule cells (Debarnardi); (*c*) aberrant epithelial rests of testis

(Monod and Terillon); (*d*) epithelium of Pflüger's tubules of the embryo (Pilliet and Cortes): (2) sarcoma, large cell or alveolar, derived from (a) Highmore's body (Ehrendorfer); (b) interstitial cells (von Hansemann, Kaufmann, Stoppato): (3) endothelioma, derived from lymph endothelium (Krompecher, Cavazzoni); (4) onesided development of a teratoma, embryonal carcinoma (Pick, Ribbert, Ewing). Sakaguchi, as the result of his own study, decided that the tumor cells are identical with spermatogonia and that they are derived from the differentiated epithelium of the tubuli contorti. The illustration of his Case 2 is interesting in that it shows definite intracanalicular growth of the tumor within the seminal tubules. In the two atypical tumors which he asserts belong to this group, the cells were somewhat smaller, the alveolar character was less distinct, and there was a greater degree of extracanalicular growth. In the malignant epithelial tumors with partly adenomatous or papillary growth, reported by him, the chief characteristic was the formation of areas of atypical glandular structures lined by cylindric epithelium, but there were also solid areas of tissue like that characteristic of the large cell tumors. He could find no evidence of a teratomatous nature and concludes, in agreement with Frank, that these tumors are derived from straight or rete tubules.

Butt and Arkin [26] (1914) give the diagnosis of sarcocarcinoma to the bilateral tumors of the undescended testes of an adult. From the description, the tumor tissue was composed of large cells arranged in solid masses and in more or less distinct tubules. Apparently the tumors in this case were of the kind which Chevassu, Frank, Sakaguchi and others believe are derived from the seminal tubule epithelium.

Cooke [27] (1915) described a metastasizing chorio-epithelioma. There were no teratomatous elements, but the origin from teratoma is considered most probable. Forty-six additional cases of chorio-epithelioma were collected from the literature, in about half of which teratomatous elements were present.

Geist and Thalhimer [28] (1917) studied the histopathology of twenty-six tumors. They make this grouping: (1) carcinoma: (*a*) medullary (alveolar, séminome), sixteen cases; (*b*) adenomatous, four cases. (2) teratoma: (*a*) without carcinoma; (*b*) with carcinoma (adenomatous, with medullary or papillomatous areas), six cases. The medullary carcinoma they derive from the spermatogonia. In the adenocarcinoma

26. Butt, A. P., and Arkin, A.: Malignant Disease of the Retained Testicle, Surg., Gynec. & Obst. **19**:419, 1914.

27. Cooke, J. V.: Chorio-Epithelioma of the Testicle, Bull. Johns Hopkins Hosp. **26**:215, 1915.

28. Geist, S. H., and Thalhimer, W.: Histopathology of Carcinoma of the Testicle, Ann. Surg. **66**:571 (Nov.) 1917.

group, the cells lining the gland spaces are smaller than in the first group, and they are cuboidal or cylindric; in the solid areas, if any cells are present, they are also smaller than in the typical medullary carcinomas. The adenocarcinomatous tumors they believe to be derived probably from the tubuli recti. The carcinomatous teratomas are usually glandular in character; they assert that they have never found carcinomatous tissue, of a kind corresponding to that of their first group, in any tumor in which the teratomatous origin was certain.

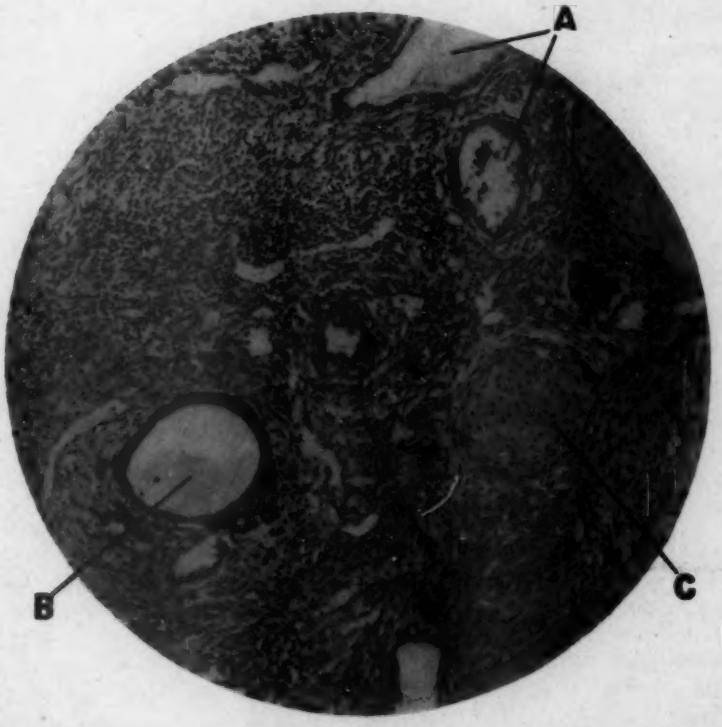

Fig. 4.—Differentiated heterologous tissue of tumor from Case 1: *A*, cystic spaces lined by cuboidal epithelium; *B*, space lined by deeply pigmented columnar epithelium; *C*, cartilage. ×80.

O'Crowley and Martland [29] (1919), as the result of the study of thirteen tumors, accept unreservedly Ewing's point of view and say that "for practical purposes there exists only one tumor of the testicle, namely, a teratoma." Of their thirteen tumors, one was a metastasizing lymphosarcoma, apparently primary in the rete or epididymis of a boy, aged 5 years, with no discoverable teratomatous elements. This

29. O'Crowley, C. R., and Martland, H. S.: New-Growths of the Testis, Surg., Gynec. & Obst. **28**:486 (May) 1919.

is the same tumor concerning whose origin from a teratoma Ewing expressed some doubt. Their second case they call a "very early lymphosarcoma." This was a mass only 1 cm. in diameter in the globus major of the epididymis of a man, aged 34. The mass contained small acini lined by cuboidal and flattened epithelium; these acini were not believed to be compressed tubules. The teratomatous nature of this tumor does not appear to be well established; if the acini present are not compressed tubules, but are neoplastic structures, the reason for calling this mass a lymphosarcoma is not very clear. The question may be raised as to whether this is really a neoplasm. Of their remaining eleven tumors, the teratomatous origin is definite in five and probable in an alveolar embryonal carcinoma of an undescended testis. The rest are large cell alveolar carcinomas, with no evidence of heterologous structure except the presence of lymphoid stroma.

It is evident that there are still wide differences of opinion as to the origin and nature of tumors of the testicle. Any histogenetic classification which attempts to include these diverse views must remain as complicated and unsatisfactory as most of the textbook classifications are today. Some unification of opinion ought to be possible, even if it is impossible to accept Ewing's conception of the teratomatous origin of practically all testicular tumors. The incentive to further study of the group of malignant tumors of the testis was given by a patient, admitted to the surgical service of the Michael Reese Hospital, whose case is herewith reported.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 30 years, eighteen months before admission, while lifting a heavy weight, felt something "give way" in the right inguinal region. At that time there was dull pain in the right side of the scrotum, but this disappeared. Enlargement of the right testicle was noticed shortly afterward; this had increased gradually and progressively until admission to the hospital. The increase in size was not associated with pain or tenderness.

Examination.—This revealed a tumor about the size of three adult fists. The surface was smooth; it was ovoid in shape, and there was a tense, elastic condition such as is found in hydrocele. The transillumination test was negative, but this was thought to be due to thickening of the sac. The preoperative diagnosis was hydrocele.

Operation.—An incision through the outer tunics of the mass evacuated a considerable quantity of slightly turbid fluid from the tunica vaginalis. A number of cystlike enlargements of varying size were seen on the exposed surface of the testis, and further exploration revealed similar changes over the entire organ. Orchidectomy, with regional removal of all lymph node bearing fat, was performed.

Pathologic Examination.—The gross pathologic report 20P670, Oct. 4, 1920, was: The specimen is an ovoid mass, 13 cm. long by 8 cm. in diameter, covered by a thickened fibrous tunic which is roughened in places externally by fibrous adhesions. The tumor (Fig. 1) is composed of tissue of varying appearance

and consistency, in which are smooth cystic cavities, the largest 4 cm. in diameter. Some areas are dense and fibrous, and contain small, pale, translucent islands which have the appearance of cartilage. Other poorly defined areas are soft, opaque, yellowish and necrotic; others are dark red, soft and fleshy; still others are soft, pale and gelatinous. At the lower pole the tunica is 0.6 cm. thick. The cord is apparently not involved.

On microscopic examination, marked variation in structure is detected, depending on the place from which the section comes and even in the same section. Large areas are necrotic. Other areas are composed of very dense, hyaline, fibrous tissue, which alternates with islands of soft, myxomatous stroma.

Fig. 5.—A large cyst in the tumor from Case 1 lined by cuboidal epithelium; beneath the latter is a heavy wall of smooth muscle. ×89.

Still other areas are very cellular. Some of these are solid, with no discernible arrangement of the cells. The latter are irregularly polyhedral, with large, vesicular nuclei; many are in mitosis; the cells are closely placed and no reticulum can be seen between them. In places the cells are cylindric and are arrranged regularly about small blood vessels. In still other cellular areas, cells of cuboidal or cylindric shape are arranged about lumens, forming atypical glandlike alveoli. All gradations are seen from the cylindric cells of the glandlike alveoli to the polyhedral cells of the solid areas. The perivascular arrangement of cells of the same origin is apparently due to papillary growth within cystic spaces which have become filled in by proliferating tumor tissue (Fig. 2). A single section, in addition to such tissue as has been here-

tofore noted, contains the following and establishes the nature of the tumor: small, well differentiated tubules, not of normal testicular type, lined by regular, tall, cylindric epithelium (Fig. 3*A*); larger, differentiated glandlike alveoli lined by cuboidal epithelium (Fig. 4*A*); several masses of squamous epithelium (Fig. 3*B*); a glandlike structure lined by a single layer of columnar epithelium which is heavily pigmented by fine black granules (retinal epithelium?) (Fig. 4*B*); wide cystic spaces lined by a single layer of low cuboidal epithelium (Fig. 5); islands of well differentiated hyaline cartilage (Fig. 4*C*); many bands and bundles of smooth muscle, which are often concentrically arranged about the cystic spaces (Fig. 5). In one section, a small island of compressed, adult testicular tissue with edematous stroma is present outside the capsule of the tumor. The epididymis is not recognizable. No tumor tissue is seen in cross sections of the cord.

The teratomatous nature of this tumor is apparent, the three germinal layers being represented by squamous and pigmented epithelium (epiblast); by glands lined by cylindric epithelium and cysts lined by cuboidal epithelium (hypoblast); and by fibrous tissue, mucoid tissue, smooth muscle, and hyaline cartilage (mesoblast). In addition to these well differentiated elements, there is atypical epithelial tissue which has all the characteristics of malignancy. The latter is glandular, papillary or solid; it is derived from the structures with columnar epithelium and is hypoblastic in origin.

There are on file in the pathologic laboratory of the Michael Reese Hospital microscopic sections from fourteen malignant tumors of the testis, in addition to those from the case herewith reported. This material has been subjected to comparative microscopic study, with these results. The original pathologic diagnosis, in quotation marks, is given in each case; this diagnosis depends somewhat on the prevailing opinion at the time the diagnosis was made and to some extent also on the individual responsible for the diagnosis. The original diagnosis is followed by our own review of the material.

CASE 2.—Path. No. 19P483, July 20, 1919.—A man, aged 24, whose right testicle had begun to increase in size one month before operation, also suffered pain in the back and a dragging sensation. There was gradual, painless increase to the size of a small orange. "Adenocarcinoma."

Comment.—This is a tumor of markedly glandular type (Fig. 6). The glands, which vary in size and shape, are lined by cylindric epithelium, and suggest a carcinoma of intestinal origin. Where the tumor is most atypical the cells become lower and more irregular and solid masses of irregularly polyhedral cells are formed. The glandular tissue often lies in an immature, spindle cell stroma, which in appearance and relation to the epithelial elements simulates closely the cellular stroma of the congenital mixed tumor of the kidney. Broad bands of denser tissue run through the tumor. These are composed of fibrous tissue, with a few bundles of smooth muscle. In these bands are small glands lined by well differentiated, nonciliated, cylindric epithelium. There are also two small, sharply defined islands of squamous cells, the central cells of each island being large and hyaline. A rounded area of considerable size in the dense tissue is composed of oval and short spindle cells with vesicular nuclei. This is young, incompletely differentiated cartilage.

There are several cystic spaces, some lined by tall columnar epithelium like that of the small glands, and others by similar epithelium which has been somewhat flattened by pressure. In some areas, the atypical glandular tumor tissue has the mucoid appearance of a colloid intestinal carcinoma. The cord contains a small mass of cells within a vessel, not glandular in arrangement, but of the same general characteristics as the solid portions of the tumor of the testis. A small mass of compressed testicular tissue is present at one side of the tumor.

In this tumor, the teratomatous nature is again apparent, although heterologous elements are not so prominent as in Case 1. Derivatives of the three

Fig. 6.—Atypical glandular structures lined by cylindric epithelium in the tumor from Case 2. × 80.

germinal layers are present. Again it is the hypoblastic derivatives which have given rise to the atypical malignant tissue, whose resemblance to an intestinal carcinoma is striking. While the stroma has an immature, spindle cell character in places, we believe that only the glandular epithelium is to be considered malignant.

Case 3.—Path. No. 20P567, Aug. 16, 1920.—A man, aged 20, suffered increase in the size of the right testis which was first noted seven years before admission. Growth was slow and gradual, and was never at any time associated with pain or tenderness. The testicle was three times the normal size; it was firm and not fluctuant (Fig. 7). "Embryonal carcinoma."

Comment.—Poorly defined cellular areas of variable size alternate with areas of fibrous and myxomatous tissue. The tumor cells are closely placed and in general are rather spindle shaped. The nuclei are oval or elongated, deeply stained and show little structural detail. A few cystic spaces of moderate size are present. These are lined by from one to three or four layers of cells which are low cuboidal when single layered; the nuclei are dense. This epithelium gives off finger-like processes into the surrounding stroma, which form solid alveolar masses embedded in the stroma (Fig. 8). In these, the cells of the outer layer are elongated; in appearance, and in relation to both the surrounding stroma and to the cells within the alveoli they resemble the cells of the malpighian layer of the epidermis. The central cells are less elongated. As this epithelium invades the stroma further from the cystic spaces from which it is derived, it goes over into the poorly defined masses which, as noted heretofore, make up the bulk of the tumor. No normal testis tissue and no teratomatous elements are seen.

In this tumor, a teratomatous origin is not apparent. It is of relatively long duration, which may have permitted overgrowth of heterologous elements by the more cellular tissue. The latter in general has the appearance of spindle cell sarcoma tissue; the morphology of some of the areas would warrant such a diagnosis. The derivation of such tissue from the low cuboidal epithelium of the cystic spaces is quite definite, and immediately about the spaces the tissue has a markedly alveolar character. The alveoli, however, are solid and nowhere partake of the glandular character seen in Cases 1 and 2. The solid alveoli resemble most closely those of a basal cell carcinoma of the skin; the cell type is also that characteristic of such a neoplasm. We believe that the cysts present in this tumor are epiblastic in origin; that the malignant tissue, in places sarcomatous in appearance and nowhere glandular in character, is derived from epiblast, and that the tumor, therefore, is teratomatous in nature.

Case 4.—Path. No. 19P881, Dec. 22, 1919.—A man, aged 46, noticed slight swelling of the testis first in September, 1919. There was gradual increase to the size of a goose egg; the increase was not associated with pain. "Embryonal carcinoma."

Comment.—This is a very cellular tumor (Fig. 9) composed of round, oval or polyhedral cells, closely placed, with no reticulum between the individual cells. Each cell has a rather wide cell body of faintly stained, coarsely meshed cytoplasm, in which is a large round or oval nucleus. The nuclei stain rather deeply, the chromatin being so finely granular that individual chromatin granules can hardly be distinguished. Each nucleus has one or two deeply stained chromatin nucleoli. The tumor cells are quite uniformly as described; few have the granular character of the nuclear chromatin so striking in developing spermatogenic cells. Narrow stroma bands run through the tumor, causing in places indistinct lobulation. At the periphery of the tumor is a thin compressed strip of testis. In this, the more peripheral cells, spermatogonia, of the tubules are identical with those of the tumor. The more central cells have the characteristic arrangement of the nuclear chromatin of spermatogenic cells. Two tubules contain a few spermatozoa; in the majority of the tubules, compression appears to have interfered with spermatogenesis. In some of the tubules, all of the cells are of the type of those of the tumor. No teratomatous elements are seen. Scattered about in the tumor tissue are irregularly

shaped islands of varying size composed of lymphocytes, which are supported on a fine reticulum. No tumor tissue is present in the cord.

This tumor was of recent origin and grew rapidly. It has throughout a markedly cellular or medullary character. In places it has an indistinct, solid alveolar arrangement, but nowhere is there any suggestion of glandlike structure. Heterologous elements are absent, unless the scattered lymphoid islands should be considered such. None of the latter has the structure of a lymphoid follicle, and all of the cells are of the ripe lymphocyte type. At the periphery, a thin layer of compressed testicular tissue is present. The description calls attention to the similarity of the tumor cells to certain of the cells of the spermatic tubules. The interpretation of this similarity will be discussed later.

Fig. 7.—Tumor from Case 3, showing the small number of small cystic spaces.

The four tumors which have just been described illustrate three types of tumor which have distinct morphologic differences. Cases 1 and 2 are alike in that both are undoubtedly of teratomatous origin. They are alike, furthermore, in that the atypical, proliferating, malignant tissue forms structures of definitely glandular character, which are apparently derived from those elements of the teratoma which are hypoblastic in origin. Case 3 appears sarcomatous in places, but is certainly epithelial. Definite proof of its teratomatous nature could not be found, but there are a few epithelial-lined cystic spaces of a kind which it is difficult to derive from normal testicular structures. The atypical tissue has developed from the lining of these cysts and forms solid, nonglandular alveoli, which appear epiblastic rather than hypoblastic in origin. Case 4 is an example of the type of tumor which has been so frequently described under a variety of names in the literature. No differentiated heterologous tissue was found. The atypical tissue present is quite different from that in

the other tumors. Of the various cell types which may occur in a teratoma of the testis or in normal testicular tissue, only the younger cells of the normal convoluted tubules bear a resemblance to the tumor cells. This resemblance is so close as to be striking. Further discussion of the possible meaning of this similarity of cell type will be delayed until other tumors of similar and different character have been described.

CASE 5.—Path. No. 5305, June 15, 1909.—A man, aged 38, had noticed painless swelling of the right testicle for three weeks. At operation the tumor was found to be the size of a large orange. "Mixed tumor of the testis showing cartilaginous, sarcomatous and atypical epithelial structures."

Comment.—There are areas of dense fibrous tissue, in one of which is an island of well differentiated hyaline cartilage surrounded by perichondrium. Large areas of branching, atypical, markedly glandular structures are lined by epithelium of the cylindric type, which is often piled up and polyhedral. Poorly defined cellular areas are composed of oval and spindle cells with relatively large, vesicular, round or oval nuclei. Embedded in these areas are numerous very large round or oval cells with finely granular, deeply eosin stained, finely fibrillated cytoplasm, each cell with from one to three or four centrally placed, round, vesicular nuclei. Some of these cells are long, narrow and longitudinally fibrillated. No cross striations can be seen, but the cells appear to be young striated muscle cells. There are a few small bundles of narrow smooth muscle cells.

CASE 6.—Path. No. 2591, June 30, 1911.—A man, aged 31, was operated on in another hospital in 1909 for left inguinal hernia and undescended left testicle. For one year before this operation, slight enlargement of the undescended testicle had been noticed. At this operation the testis was brought down into the scrotum but later it retracted into the inguinal canal. Increase in the size of the testicle, which became apparent in 1910, was rapid; it was not associated with pain, but with loss of weight. "Malignant embryoma."

Comment.—Most of the tissue is so completely necrotic that its nature cannot be determined. Broad bundles of dense fibrous tissue are partly infiltrated by polymorphonuclear leukocytes. Some of these bands, which contain narrow bundles of smooth muscle, come apparently from the epididymis. There is a single small, well defined island of cartilage. In some of the fibrous tissue bands there are a number of cystic spaces; some are empty, some are filled with necrotic material, some contain fragments of cells and one is partly lined by single layered, low cuboidal epithelium. Embedded in the fibrous tissue is a poorly defined cellular area composed of oval and round cells with vesicular or elongated nuclei. In this area are a few atypical gland-like structures lined by cylindric epithelium.

CASE 7.—Path. No. 3331, Jan. 29, 1912.—A man, aged 23 years, one month before admission, had noticed a firm, small nodule of the right side of the scrotum. This enlarged rapidly and painlessly to the size of a small orange. "Carcinoma sarcomatodes."

Comment.—At the periphery is stroma which contains small glandlike structures lined by tall cylindric cells and wide cystic spaces lined by cuboidal epithelium. In both kinds of structure the epithelium piles up in places and forms masses of polyhedral cells which invade the stroma, where the masses are often separated from one another by blood and fibrin. These masses are of variable size and shape. Cellular outlines are indistinct or absent, giving

to the tissue the appearance of syncytium. The cells, when they are not fused, are large and irregularly polyhedral, with large vesicular nuclei which have distinct membranes but little chromatin. The cord is inflamed and invaded.

Case 8.—Path. No. 4513, Jan. 7, 1913.—A man, aged 33, had suffered pain and swelling of the left testis for six weeks. The size of the tumor is not stated. It was firm, not nodular. "Primary carcinoma."

Comment.—Large, solid, cellular alveoli are surrounded by dense, broad bands of fibrous tissue and smooth muscle. The cells are large and irregularly polyhedral. The nuclei are large; each has a distinct membrane and little finely granular or coarser chromatin on a loose reticulum; the nucleolus is

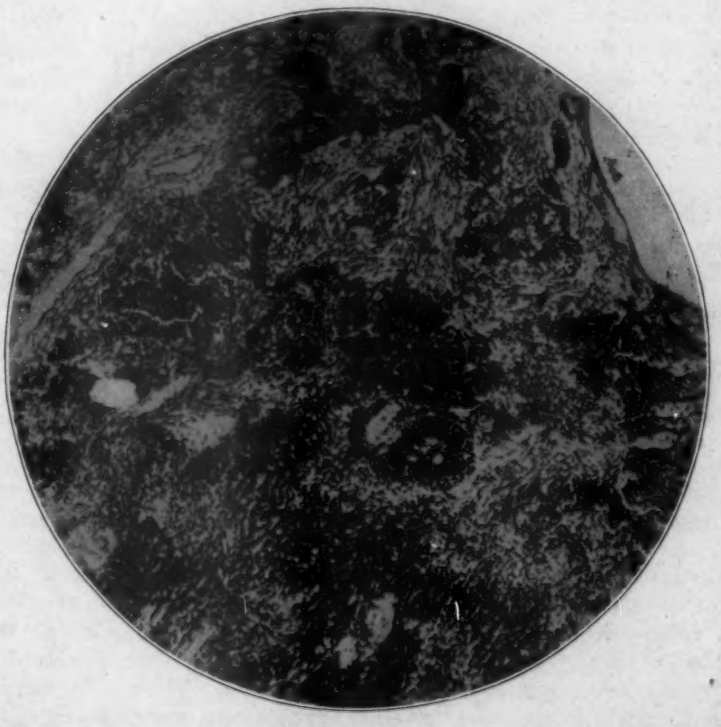

Fig. 8.—The margin of one of the small cystic spaces of the tumor from Case 3. This is lined by cuboidal epithelium, from which solid cellular alveoli are given off and penetrate the stroma. ×80.

distinct and deeply stained. The nucleus is surrounded by a broad zone of coarsely alveolar cytoplasm. The larger alveoli are subdivided by narrow stroma bands which run in from the periphery. A mass of tumor cells is present in a larger artery. A few small alveoli in the dense tissue have a somewhat glandular appearance and are lined by cells of the cylindric type. At the periphery of some of the large, solid alveoli, the cells may be rather regularly arranged, with a shape approaching cylindric. Some of the large alveoli have several lumen-like spaces, about which the cells are more regularly arranged and are columnar. Many large alveoli are centrally necrotic. There

is much dense stroma in one area, with many lymphocytes and bundles of smooth muscle. There is a mass of atrophic testicular tissue near this area.

Case 9.—Path. No. 8531, Feb. 9, 1916.—A man, aged 23, had suffered hypogastric pain with frequent micturition for two years. He had lost 20 pounds in weight in the last five weeks before admission. Neither testicle was in the scrotum. At operation, a mass the size of a grapefruit was found in the small pelvis; this was a tumor of the undescended left testicle. "Mixed tumor, teratoid not teratoma, malignant."

Comment.—Dense stroma encloses cystic spaces and smaller glands lined by cuboidal or cylindric, nonciliated epithelium. Atypical, glandular, adenocarcinomatous tissue is composed of hyperplastic and irregular epithelium derived from that of the spaces. There is much necrosis. No teratomatous structures and no normal testis tissue are seen.

Case 10.—Path. No. 9447, Nov. 15, 1916.—A man, aged 38, had experienced sudden pain, following intercourse, in the left testis six months before admission. Slight swelling of the testicle was noticed the next day. The pain disappeared, but the testis increased progressively in size until it was as large as an orange. The mass had been needled twice. There was some pain during the last two weeks before admission. After removal, the tumor measured 12 by 10 by 6 cm.; the cut surface showed dark gray areas of hemorrhage and necrosis. "Malignant teratoma."

Comment.—The tumor is of definitely mixed character and contains areas of differentiated hyaline cartilage, fibrous stroma, many large bundles of smooth muscle and islands of squamous epithelium. Cystlike spaces of variable size are lined by cuboidal to cylindric epithelium; in some of these spaces the epithelium is ciliated. Glandlike spaces of varying size and shape are lined by very tall, well differentiated, columnar epithelium, which is not ciliated and which has the appearance of intestinal epithelium. In some cystic spaces, direct transformation from single layered cylindric epithelium to many layered squamous epithelium can be seen. In some of the larger glands, the epithelium forms papillary infoldings. In one area, the epithelial tissue is still glandular, but atypical; its variable and irregular cells are apparently derived from the cylindric epithelium. In places these cells form irregular syncytial masses. Some of the glands with differentiated columnar epithelium lie in very cellular stroma composed of oval and spindle cells. Embedded in the more differentiated stroma are small, irregularly alveolar masses of cells with densely stained, solid nuclei and with very little cytoplasm. These cells are larger than lymphocytes; in appearance and in their indistinct rosette arrangement in places, they suggest neuro-epithelial tissue.

Case 11.—Path. No. 1890, Nov. 18, 1910.—A man, aged 39, gave a clinical history of chronic appendicitis. He had been operated on for double inguinal hernia eleven years previously. After recovery from this operation, he noticed only one testicle in the scrotum and was told by the surgeon that he had had only one descended testis, the other being left in the inguinal canal. At the last operation, the right testis was in the scrotum. A tumor mass about the size of an orange extended from the umbilicus to within 1 inch of the pubis; this was a tumor of the undescended left testis. "Large, round cell sarcoma."

Comment.—Narrow stroma bands form a supporting network and subdivide the cellular tumor into polyhedral alveoli. In areas, the alveoli are small and have somewhat the appearance of solid seminal tubules. The cells are large

and have the general morphology of spermatocytes. The chromatin is in the form of fine granules on a distinct network.

Case 12.—Path. No. 2605, July 3, 1911.—A man, aged 41, had experienced increase in the size of the right testicle, without pain, for one year. At operation, the right testis was found transformed into an irregularly nodular mass the size of a small orange. "Round cell sarcoma."

Comment.—This is a very cellular tumor, with a small amount of stroma. The cells usually show no regular arrangement, but sometimes form indefinite clumps, and rarely are aggregated into groups by confining bands of reticulum.

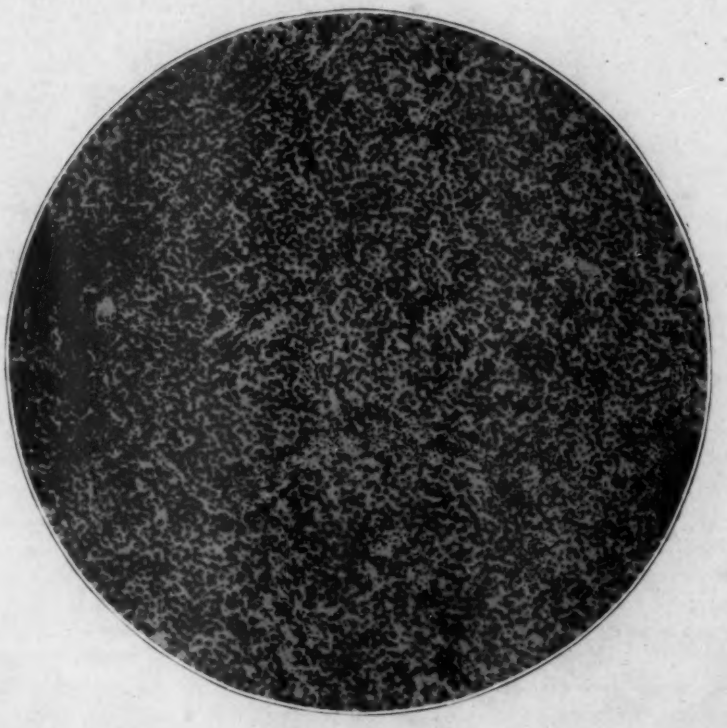

Fig. 9.—The large celled, indistinctly alveolar tissue of the tumor from Case 4. At one side is an island of lymphocytes. × 80.

The cells are large, round or polyhedral, with a rather wide zone of dense, finely granular cytoplasm. The nuclei are large. In some, the chromatin is in fine granules on a close reticulum. In others, the granules are larger and are more widely separated. Some large nuclei are deeply hyperchromatic. Some nuclei are small and pyknotic. An occasional nucleus is narrow, small, pyknotic, and suggests a sperm head. Tumor cells are present within a large vein which is surrounded by dense fibrous tissue.

Case 13.—Path. No. 4204, Oct. 8, 1912.—A man, aged 45, had noticed pain and swelling of the left testis for seven weeks, with gradual increase to the size of a small orange. The pain was only slight. The mass was firm and only slightly tender on pressure. "Small, round cell sarcoma."

Comment.—Very cellular tumor tissue has replaced all the original elements. It is composed of rather large, round, oval or slightly elongated cells, each of which has a narrow zone of faintly stained cytoplasm and a relatively large nucleus. The nuclei have a homogeneous appearance, due to the uniform distribution of minute chromatin granules throughout the nucleus. A nuclear reticulum can not be seen. Most of the nuclei contain one or two small indistinct nucleoli. Some nuclei stain more deeply than others. The closely placed cells form indistinct alveolar nests and solid cords, from two to four or five cells wide, separated by narrow bands of reticulum. In a few places, small, solid alveolar masses are surrounded by definite fibrous walls, apparently as the result of the growth of tumor tissue within blood vessels or tubules. Areas of the tissue are necrotic. No glandular structures and no teratomatous elements are seen. The cord is inflamed; some arteries are obliterated by inflammatory tissue; an occasional one contains a mass of cells like the tumor cells.

Case 14.—Path. No. 5096, June 18, 1913.—A man, aged 33, had first noticed enlargement one year before admission. The increase continued without pain. The patient's blood gave a ++++ Wassermann reaction. At operation, the left testicle was found to be nodular, firm and the size of a hen's egg. "Mixed round cell sarcoma."

Comment.—Large, solid, cellular areas are subdivided by very fine strands carrying capillaries into indistinct polygonal alveoli. The cells are large, irregularly polyhedral and have a considerable amount of granular cytoplasm. The nuclei are large and round, with marked chromatin variation. Some are solid and hyperchromatic. Others are vesicular, with finely granular chromatin on a close meshwork. In other nuclei, the chromatin granules are coarser and are more regularly arranged about the inner surface of the membrane on a more widely meshed reticulum. The cells vary considerably in size. Many of the smaller ones have solid, deeply stained nuclei.

Case 15.—Path. No. 7817, July 25, 1915.—A man, aged 42, had had swelling of the left testis of five weeks' duration, some tenderness, but no pain. The patient asserted that the increase in size began suddenly and reached three times the normal size of the testis in one week, since which time the size had remained stationary. The clinical diagnosis was tuberculous epididymitis. At operation, both the left epididymis and testicle were found to be enlarged and largely replaced by caseous yellow material. "Primary sex cell tumor."

Comment.—Broad dense stroma bands, which are infiltrated by lymphocytes, subdivide the tissue and surround large, solid, cellular areas. The cells are large, round, oval or polyhedral, closely placed, and have little cytoplasm. The nuclei are large, rich in chromatin, round or oval. The nuclear chromatin is finely granular and is uniformly distributed throughout the nucleus. In most of the nuclei, there is a small, indistinct nucleolus. In some areas, the cells form anastomosing bands which lie in cellular young stroma. There is no glandular arrangement anywhere; and no teratomatous elements are seen. There are large areas of necrosis, about which the tissue contains many polymorphonuclear leukocytes.

GENERAL CONSIDERATION OF CASES

Cases 5 to 15, inclusive, again fall into three groups. In Cases 5, 6 and 10 the presence of heterologous tissue elements establishes the

teratomatous origin of the tumors. Of the greatest importance is the fact that the atypical tissue has a glandular character and is apparently hypoblastic in origin. These three tumors, therefore, are identical with Cases 1 and 2. Cases 7, 8 and 9 form a second group, in that the teratomatous nature can not be definitely established by the presence of heterologous differentiated tissues. But each of these tumors contains, in varying numbers, glandular or cystic structures which are lined by single layered, well differentiated epithelium. These structures, which apparently represent the benign stage of the epithelium from which the atypical tissue comes, have no analogy with any of the structural elements of the normal testis. They are, however, much like some of the glandular elements present in the teratomatous tumors of Cases 1, 2, 5, 6 and 10. Furthermore, the atypical tissue of Cases 7, 8 and 9 is of the same general character as that of the teratomatous tumors. We, therefore, believe that Cases 7, 8 and 9 are to be grouped with Cases 1, 2, 5, 6 and 10 as malignant epithelial tumors which originated in teratomas. From a study of these tumors we believe that the glandular or adenocarcinomatous character of the malignant tissue of testicular tumors is the best criterion of the teratomatous origin of such tumors. In view of the fact that tumors with undoubted heterologous elements almost always give rise to atypical tissue of this sort, we cannot concede the derivation of tumors, which contain the same kind of atypical tissue but no heterologous elements, from the tubuli recti, but agree with Ewing [1] that such tumors are the result of the onesided development of some one constituent of a teratoma. This constituent, we believe to be smaller differentiated glandular or larger cystic structures which are hypoblastic in origin. To the same general group belongs Case 3, already considered above. This we believe to be a malignant epithelial tumor derived from the epiblastic elements of a teratoma.

The tumors of Cases 11, 12, 13, 14 and 15 form a quite distinct group, to which belongs also Case 4, which was selected for more detailed discussion above. Common to all these tumors is their soft, cellular, medullary character, which has been responsible for the widespread use of the term "large round cell sarcoma" for neoplasms of this kind. An alveolar arrangement of the cells can usually be detected; in some examples, it is quite distinct in places, while in others an alveolar character is more difficult to determine. In none of the tumors is there any semblance of a glandular arrangement. In not one of the six tumors of this group in our series is heterologous tissue present. This seems to hold also for the large cell tumors described by others. Dense groups of lymphocytes occur frequently, but they do not have the appearance of true lymphoid tissue. Most characteristic, and most important for any attempt to elucidate the origin of tumors of this

group, is the type of the tumor cell. The latter is large. It is irregularly polyhedral in shape, due to the pressure which the cells exert on one another. The cytoplasm stains faintly and is rather coarsely alveolar. The nucleus is absolutely and relatively large and has a distinct membrane and one or two indistinct, small nucleoli. The chromatin, in different tumors and sometimes in the same tumor, shows differences in arrangement and distribution, but these differences all fall into a definite series. In some tumors, of which Cases 4, 13 and 15 are examples, distinct chromatin granules do not occur or are so fine that they cannot be readily seen. Such nuclei stain with moderate intensity and have a homogeneous ground-glass appearance. Apparently the chromatin is dissolved in the karyolymph or is uniformly distributed in the latter in the form of very fine granules. In other tumors, Case 11 for example, the chromatin is aggregated into distinct but still small granules, which are arranged on a finely meshed intranuclear network. In still other tumors, Cases 12 and 14, the granules are still larger and fewer in number, as the result of further aggregation and condensation of chromatin on the intranuclear network, which is now more coarsely meshed. In addition to these nuclear types, every tumor contains a large or small number of solid, deeply hyperchromatic nuclei. There may be variation in nuclear size, a small proportion of nuclei being larger than the average, but with the typical chromatin distribution, a somewhat larger proportion being smaller than the average. It is more especially the hyperchromatic nuclei which have the smaller diameters.

The nuclear morphology which has been described appears to be very characteristic of the group of tumors under consideration. Malignant tumors of definite teratomatous origin may be composed of large cells with relatively large vesicular nuclei, but such nuclei are quite distinctly different, in that they have the characteristics of young tissue nuclei. The nuclear type under consideration is not found in normal somatic nuclei, either young or old, but it is characteristic of the sex cells of the seminal tubules. The homogeneous nucleus first described is identical with that of the spermatogonia; the two kinds of cell cannot be distinguished from each other when tubules and tumor tissue can be studied side by side in the same section. The finely granular, closely meshed nucleus is like that of the early spermatogenic cell or spermatocyte as it is proceeding to mitosis; and the more coarsely granular, loosely meshed nucleus corresponds to that of the spermatogenic cell just before the chromatin becomes formed into definite chromosomes. These granular stages are very much like the leptotene and pachytene stages in the spermatogenesis of those lower animal forms whose spermatogenic cycle has been carefully studied. The smaller, more con-

densed and hyperchromatic nuclei present in considerable numbers in the cells of some tumors are suggestive of the later stage in spermatogenesis just before the spermatid nucleus elongates to form the head of the spermatozoon. Two of our tumors contain a few scattered groups of elongated, densely stained nuclei, very much like, but larger than, the elongated nuclei of the late spermatid stage. Because these may be the result of degenerative phenomena in the tumors, we hesitate to consider them true derivatives of the tumor cell cycle. Not only do the various cells described bear the greatest resemblance to the cells of the spermatogenic cycle, but the converse is also true. The nuclei bear no resemblance to those of normal somatic cells or to those of tumors derived from somatic cells.

Of the kind of tumor under discussion, Ewing [1] says: "The typical large cell tumor of the testis, with large, round, clear cells and lymphoid stroma, is a highly characteristic structure which is duplicated by no other structure." In this we agree with him, but we believe that the highly characteristic feature relates to the nuclei rather than to the cells or to their arrangement. Our series of tumors does not bear out his further statement that "this characteristic tumor is exactly the type of carcinoma which occurs in the complex teratomata of the author's series." We are unable to find in our tumors of this group any type of tissue which would warrant the assumption of origin from teratoma. More important than such negative evidence is the peculiar nuclear type, which is not found in any of the other tumors, but which is characteristic of the cells of the seminiferous tubules. We can find no evidence of transition from the cellular tissue of definitely teratomatous tumors to cells of this type. In the summary of Geist and Thalhimer's [28] article, the following statements are made: "The common type of carcinoma associated with teratoma is adenomatous in character. The medullary tumors we believe are primary tumors of the testicle arising from the seminiferous tubules." With these conclusions we are in entire accord. We would, however, go a little further and state our conviction that all testicular tumors of adenomatous character are teratomatous in origin, in spite of the fact that heterologous elements are not detected in some of the tumors of this character. The evidence that such tumors are derived from the tubuli recti, as asserted by Geist and Thalhimer, Frank and others, appears inadequate. For the malignant epithelial tumors of certain or probable teratomatous origin, Ewing's designation of them as embryonal carcinoma seems the best. For the large cell, medullary tumors, which in agreement with Chevassu, Frank, Sakaguchi, Geist and Thalhimer and others, we hold to be derived from the epithelium of the seminiferous tubules, a name which would indicate their origin from cells of the spermatogenic cycle

appears preferable. We suggest spermatocytoma as perhaps better than the séminome of Chevassu.

The fifteen tumors, all malignant, studied in this series subdivide themselves thus: Five with definite heterologous structures, the atypical tissue being hypoblastic in character; three without heterologous elements, but with atypical tissue of the hypoblastic type; one without heterologous elements, but with atypical tissue probably of epiblastic origin; six spermatocytomas, all without heterologous tissue. Believing that tumors of hypoblastic or epiblastic type are derived from teratoma, all the tumors can be divided into two groups, which will cover all the malignant tumors of the testis of clinical importance: I, embryonal carcinoma, which would include nine of our tumors and II, spermatocytoma, which would include six of our tumors. The age incidence in these two groups is suggestive. In the first group, the ages in years are as follows, the number of tumors at each age being given in parentheses after the age: 20 (one), 23 (two), 24 (one), 30 (one), 33 (one), 38 (two). In the second group the ages are: 33 (one), 39 (one), 41 (one), 42 (one), 45 (one), 46 (one). In the first group the average age is 29 years; the average is raised by the two tumors at 38 years, all the rest occurring at 33 years or under. In the second group, the average age is 41 years; the average is lowered by a single tumor at 33 years, all the rest being at 39 years or more. If these extreme cases are omitted, the average age in the two groups is, respectively, 26.3 years and 42.6 years. The higher average age incidence of the second group is not due to a longer clinical duration of the tumors of this group; on the contrary, the rate of growth of the tumor is more rapid and the duration shorter in the second group than in the first. Far-reaching conclusions are not permissible from this small number of cases, but the difference in age deserves some consideration when it is correlated with the histologic differences which we consider fundamental. In this connection, it is to be noted that Hardouin and Potel [30] have reported a tumor which they consider a seminoma in a boy, aged 7 years.

Our series includes examples of the different kinds of malignant epithelial tumors except chorio-epithelioma. In three of the glandular, hypoblastic tumors, syncytial cell masses are formed; but these appear to be the result of the same process which leads to cell fusion in rapidly growing carcinomas of the mammary gland and intestine. True chorioma must be derived from embryonic membrane tissue and the explanation of the origin of this form of neoplasm must be based on a satisfactory and acceptable theory of the origin of teratoma of the testis in general. The various theories have been critically analyzed by

30. Hardouin, P., and Potel, G.: Deux observations de tumeur du testicule chez l'enfant, Bull. et mém. Soc. anat. de Paris **79**:150, 1914.

Ewing.[1] He accepts, as subject to the fewest objections, the theory of the origin of teratoma from sex cells. Whether this derivation is from sex cells whose normal development into spermatogonia has been suppressed, as held by Ewing, or from normal sex cells by a process of parthenogenesis, is a question which is impossible of solution in the present state of our knowledge. Origin by parthenogenesis from normal sex cells appears to us to offer fewer theoretical objections than origin from suppressed dormant and undeveloped sex cells. Granted that a teratoma may arise in the testis from a sex cell, either normal or suppressed, then the development of fetal membrane epithelial tissue and of chorioma offers no difficulties, since trophoblast might well be the very first tissue element formed. If the trophoblastic tissue should go on to unrestricted proliferation at this early stage, a pure chorioma without any differentiated teratomatous elements might result, but such a tumor would still have to be considered teratomatous in origin. In Cooke's [27] tabulation of forty-seven chorio-epitheliomas, heterologous tissues were said to have been present in about half. When this combination of chorioma with differentiated tissues of other kinds occurs, the choriomatous tissue must be the result, not of the reversion of differentiated cells of the teratoma, but of the progressive proliferation of trophoblastic tissue which has failed to disappear in the further development of the teratoma. According to this conception, chorioepithelioma of the testicle would fall into the first of the two groups which we have made heretofore, namely, embryonal carcinoma of teratomatous origin. Hartmann and Peyron [31] conclude that the structural differences which embryomatous tumors show are dependent on the stage of development which the ovum or totipotent cell reaches before malignant proliferation begins, a view which is not opposed to that expressed. The term placentoma, introduced by them for a group which they distinguish from chorioma, does not appear applicable to testicular tumors and should be reserved, if it is used at all, for tumors originating from decidual tissue. We cannot agree with Glaserfeld [32] that the fetal ectoderm, metastasizing as such, may give rise at some point distant from the primary tumor to chorionic epithelium as well as to other ectodermic structures, although we do not preclude the possibility of the formation of syncytial masses from ectodermal tissue. The mere formation of multinucleated protoplasmic masses without distinct cell boundaries does not constitute chorioma. The formation of such syn-

31. Hartmann, H., and Peyron, A.: Placentomes et choriomes du testicule, Bull. Acad. de méd. **81**:733 (June 3) 1919. Sur les néoformations d'origine chorioectodermique dans les tumeurs du testicule, Compt. rend. Acad. d. sc., Paris **168**:1131, 1919.

32. Glaserfeld, B.: Ueber das Hodenteratom mit chorionepitheliomähnlichen Bildungen, Ztschr. f. Krebsforsch. **9**:570, 1910.

cytial masses is a property of a wide variety of cells other than those of the fetal membrane epithelium.

Since the testicle contains various kinds of mesoblastic tissues in addition to the specific tissues which give rise to the tumors considered, any classification of tumors of the testis must include the various possibilities and must therefore be somewhat complicated. In the suggested classification which follows, only the two groups that are italicized are of clinical importance; the remaining headings, which may be disregarded for practical purposes, are included merely to give a place for tumors whose origin from elements other than those of teratoma or seminiferous tubules may be considered definitely established:

I. Homologous Tumors:
  A. Benign:
    1. Epithelial:
      (*a*) Adenoma of the seminal tubules (the tumors of Chevassu and of Pick [Ewing[1]]).
    2. Mesoblastic:
      (*a*) Fibroma (arising in the tunics; the tumors of Lardennois and Lecène,[15] Makins[16] and Boyer[17]).
      (*b*) Leiomyoma (arising in the epididymis; Ewing[1] accepts the tumors of Trelat, Rindfleisch, and Hericourt; a specimen recently received by the pathologic laboratory of the Michael Reese Hospital is a tumor of the epididymis of this kind).
      (*c*) Vascular tumors (lymphangioma, hemangioma).
      (*d*) Interstitial cell tumors. (A specimen in his own laboratory and the case reported by Chevassu, Ewing[1] considers examples of hyperplasia rather than neoplasia.)
  B. Malignant:
    1. Epithelial:
      (*a*) *Spermatocytoma.*
    2. Mesoblastic:
      (*a*) Sarcoma. (Extremely rare; possibly Sakaguchi's[28] case and three of Miyata's[19] cases arising in the tunics may be accepted.)

II. Heterologous Tumors:
  A. Benign:
    1. Cystic dermoid.
  B. Malignant:
    1. *Embryonal carcinoma.* Heterologous tissue may be present or may have been overgrown. The atypical tissue may be:
      (*a*) Trophoblastic (chorio-epithelioma).
      (*b*) Hypoblastic (the usual adenomatous tumor).
      (*c*) Epiblastic (solid alveoli of basal cell type, or tumors of neurocytoma type).
    2. Sarcomatous mixed tumor (true sarcoma in a teratoma appears to be rare).

CONCLUSIONS

In malignant tumors of the testicle, heterologous tissues may be present or absent. In the former case, the teratomatous nature is established. Tumors without heterologous elements may or may not be derived from teratoma.

In malignant tumors whose teratomatous origin is undoubted, the atypical tissue usually has a glandular character, suggestive of derivation from hypoblastic epithelium. In a certain proportion of tumors without heterologous tissue, the atypical tissue is of the same glandular character. Such tumors are derived from hypoblastic epithelium, whose proliferation has suppressed or overgrown such teratomatous structures as may have been present, or the malignant proliferation may have begun so early that differentiated mixed tissues were not formed.

In another group of tumors, the atypical tissue may have the characteristics of chorionic epithelium. In about half of the reported tumors of this group, heterologous elements were present and establish the teratomatous origin. Chorioma arises from the trophoblastic constituents of a teratoma. This may occur at so early a stage that histioid or organoid structures have not been formed, or at a later stage. In the latter case the heterologous elements may persist, or they may be overgrown by the choriomatous tissue.

In a small group of tumors, origin from the epiblastic constituents of a teratoma appears probable. The atypical tissue may have the structure of basal cell carcinoma or of neurocytoma.

For those tumors whose teratomatous origin is either definitely established by the presence of heterologous elements or is rendered very probable by the character of the atypical tissue, the designation embryonal carcinoma should be accepted. This term may be modified by the adjective hypoblastic, trophoblastic or epiblastic if the atypical tissue is glandular, syncytial or solid.

Quite distinct from the embryonal carcinomas are the tumors of the solid, medullary, large cell type. The distinguishing characteristic of these tumors is the cell type. The tumor cell is morphologically identical with the younger cells of the spermatogenic cycle and is probably derived from the cells of the seminiferous tubules. For this kind of tumor the term spermatocytoma is suggested.

In our series, none of the tumors which we have considered to be spermatocytomas contains any heterologous elements, nor does the atypical tissue have the morphology of that of any of the embryonal carcinomas.

In our series, the age incidence of spermatocytoma is distinctly higher than that of embryonal carcinoma; the clinical duration is shorter and the course is more rapid.

The very great majority of malignant tumors of the testicle are epithelial and are either embryonal carcinomas or spermatocytomas.

The term sarcoma, as a designation for malignant testicular tumors, should be discarded unless the derivation of the tumor from mesoblastic tissue can be established. This applies particularly to alveolar sarcoma, large round cell sarcoma, globocellular sarcoma, angioplastic sarcoma, etc., which are names that have been improperly applied to tumors of the spermatocytoma group. The peritheliomas, hypernephromas and interstitial cell sarcomas probably all belong to this group.

Homologous pure tumors of the testis, except spermatocytoma, are rare. A few fibromas, leiomyomas, and spindle cell sarcomas, arising in the epididymis or in the tunics of the cord, epididymis or testicle may be accepted.

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ACCESSORY PANCREATIC TISSUE

REPORT OF TWO CASES *

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The occurrence of accessory pancreatic tissue in man is rather uncommon; a careful review of the literature by Warthin [1] in 1904 revealed only forty-seven cases, to which he added two. One case was reported in 1894 by Biggs,[2] which was not included in Warthin's survey, since which thirty-one additional cases have been reported (Table 1). Twelve of these thirty-two cases were found at operation, the remainder at necropsy.

In a series of 321 consecutive necropsies in the Mayo Clinic in which the entire length of the intestine was opened in 314 cases, I found accessory pancreases in two cases (0.6 per cent.). In one case the aberrant tissue was in the stomach; in the other, in the duodenum. These statistics conform to Opie's,[3] who found ten cases of aberrant pancreatic tissue in 1,800 necropsies. In several instances, I have observed accessory pancreatic tissue in the jejunum at operation. In one instance, it was about 3 inches from the ligament of Treitz opposite the mesentery, and it was necessary to go below it in order to perform a gastro-enterostomy.

A macroscopic and microscopic study of the two specimens of accessory pancreatic tissue that I found at necropsy forms the basis of this investigation. I have, in addition, reviewed the embryology of the pancreas in an effort to ascertain the cause of abnormally situated masses of pancreatic tissue.

SPECIMENS OF ACCESSORY PANCREATIC TISSUE

CASE 1 (139972).—At necropsy on a woman, aged 64, a small tumor was found in the duodenum, 5.5 cm. below the pylorus and 3 cm. above the papilla of the common bile duct. The base of the tumor was 1.5 cm. by 1.5 cm., and it projected 1 cm. into the lumen of the bowel (Fig. 1). Microscopic examination disclosed it to be an aberrant mass of pancreatic tissue. All the histologic structures of the pancreas were present, namely, ducts, acini, islets and connective tissue. The growth was covered by the mucous membrane of the duodenum and appeared to be embedded in the submucosa.

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1. Warthin, A. S.: Two Cases of Accessory Pancreas (Omentum and Stomach), Physician & Surg. **26**:337-340, 1904.

2. Biggs, G. P.: Supernumerary Pancreas in the Pylorus, Proc. New York Path. Soc. 1894, pp. 55-56.

3. Opie, E. L.: Disease of the Pancreas, Its Cause and Nature, Ed. 2, Philadelphia, J. B. Lippincott Company, 1910.

CASE 2 (130601).—At necropsy on a woman, aged 21, on the posterior wall of the stomach near the greater curvature, in the prepyloric region, a hemispherical tumor mass was found, with its rounded surface covered by mucous membrane, projecting into the lumen of the stomach (Figs. 2 and 3). The base was 3 cm. by 2.5 cm., the thickness 1.2 cm. On section, the cut surface of the tumor was pinkish-white with many small lobules. A rich blood supply was manifested by several large blood vessels. The tumor had the appearance of pancreatic tissue. Microscopic study verified the macroscopic diagnosis by the finding of pancreatic acini, ducts, islets, and connective tissue in about the same relation as in the normal pancreas. Its bases rested on the submucosa and its rounded surface was covered over by the muscularis mucosae and mucous membrane.

HISTOLOGIC APPEARANCE OF THE SPECIMENS

In both specimens, all the histologic units of the pancreas were identified under the microscope, namely, ducts, acini, islets, and connective tissue (Figs. 4, 5, and 6). In Specimen 1, all the microscopic sections examined showed an increase in the interlobular, interacinar and periductal connective tissue. In Specimen 2, all the sections presented the well known microscopic picture of the normal adult pancreas.

Ducts.—Each specimen contained one large duct, which was patent, lined with high columnar epithelium, with an outer coat of dense fibrous tissue, and which I believed to be the main excretory duct. Into this outer coat the interlobular ducts passed obliquely as they do in the normal gland, an observation which I had made previously.[4]

Acini.—The arrangement of the cells forming the acini was the same as in the normal pancreas. These large secreting cells are pyramidal in shape and resemble the normal acini cells. The so-called centro-acinar cells were present.

Islets.—In Specimen 1, the islets were small and few in number, and there was a moderate fibrosis. In Specimen 2, the islets were numerous. They were normal in size and the cells resembled those of the normal islet.

In order to determine whether the acinic cells in the alveoli had been functioning, and if so to demonstrate their activity of function, sections were stained for zymogen. Sections from both specimens were found on microscopic examination to contain large zymogen granules in the cytoplasm of the apical portion of the acinic cells (Fig. 7).

The presence of zymogen granules in the acinic cells and a patent excretory duct are sufficient evidence to prove that these tissues were producing pancreatic juice; and by the presence of the islets, one is justified in concluding that they were producing a hormone, which was the same as the internal secretion from the islets in the pancreas. These observations make it reasonable to assume that aberrant masses of pancreatic tissue are capable of the same function as the normally placed gland and that they function independently of it.

EMBRYOLOGY

A careful study of the embryology of the pancreas in the minute human embryo [5] has been possible only in a few instances, and most of

4. Horgan, E. J.: The Histogenesis of Carcinoma in the Islets of the Pancreas, J. Lab. & Clin. M. **5**:429-442 (April) 1920.

5. Lewis, F. T.: Development of the Pancreas, in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912 **2**:429-445.

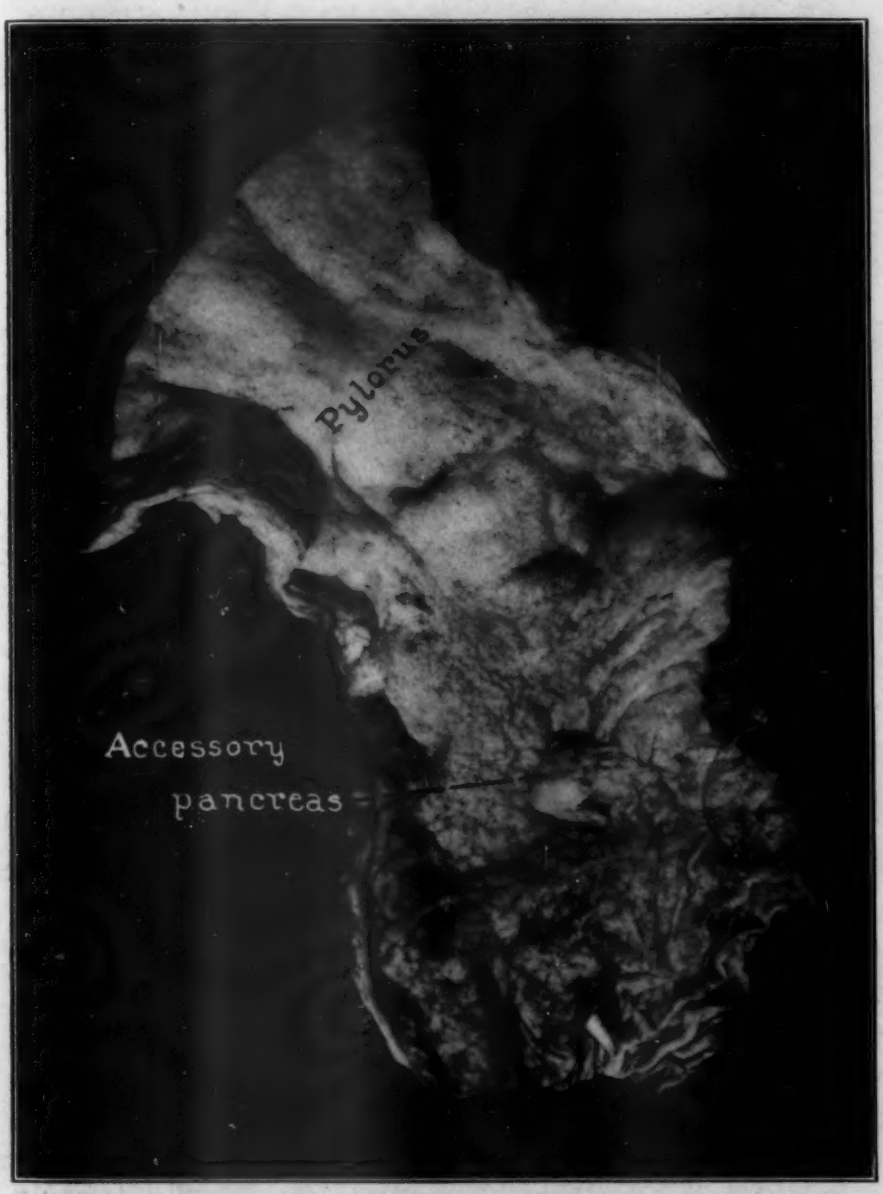

Fig. 1 (A129972).—Accessory pancreas in the duodenum 5.5 cm. below the pylorus (Probe point may be seen projecting through ampulla of common bile duct).

the data are from the study of the development of the pancreas in the lower vertebrates. For this reason and because an accessory pancreas in the dog has been reported by Mann,[6] I reviewed the comparative anatomy and embryology of the pancreas.

Comparative Anatomy and Embryology.—From the researches of Oppel [7] and a complete survey of the literature which was compiled and reviewed by him, we have recorded data to prove the occurrence of the pancreas in the vertebrata from the cyclostomes, the lowest form of fish, through the orders of fishes, amphibians, reptiles, birds and mammals, to man. For a long time it was believed that the pancreas was missing in fishes and amphibians, but the organ has been found in many species

Fig. 2 (A130601).—Accessory pancreas in the posterior wall, near the greater curvature, in the prepyloric region of the stomach.

of these two orders. Oppel believes it could be found in every species of vertebrate if the investigator would make an earnest search for it.

It is of interest to know that even though Oppel made serial cross sections of the entire animal he could not demonstrate a pancreas in *Amphioxus lanceolatus,* the animal which is the only species representing the order of acranial vertebrates and spanning the gap between the vertebrates and the invertebrates. Other organs are missing in this animal and the pancreas may be. Oppel leaves it an open question.

6. Mann, F. C.: Accessory Pancreas in the Dog, Anat. Record **19**:263-268, 1920.

7. Oppel, A.: Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere. Jena, Fischer, 1900. **3**:742-870.

No doubt the extreme variation in the form of the pancreas in different species of animals has been the cause of its being overlooked by some investigators, for there is no regularity of form for each order of vertebrates. Oppel and others have found that the gland may exist in the form of (1) single or multiple masses of gland tissue embedded between the muscularis and serosa in the wall of the stomach or duodenum, or both, and having one or more short or long ducts from each mass; (2) one or several gland masses spread out between the layers of the mesentery and attached to the stomach, duodenum, or intestine and emptying through one main excretory duct from each mass; (3) numerous small or very small glands in fine cordons dispersed throughout the entire

Fig. 3 (A130601).—Cut surface of bisected accessory pancreas in the wall of the stomach showing lobules and blood vessels.

cavity between the layers of the mesentery, or, (4) numerous small or very small glands growing along the blood vessels, enveloping them like a sheath, and advancing with the blood vessels into the liver and spleen, interweaving the liver as it follows the vessels in their various directions, or into the spleen by entering at the hilum with the blood vessels, or spreading over the splenic capsule from the hilum.

In man, the fully developed gland is constantly found to lie in a transverse position, firmly fixed against the spine with the head engaged in the concavity of the first portion of the duodenum, while in many of the mammals, it is rather loosely placed between the layers of the mesentery of the small intestine and distributed over a large area.

Cells believed to be islet cells have been described as occurring in the gland tissue of all the various species in which the pancreas has been

studied. In the fishes, amphibians and reptiles, they occur in groups of a few cells only, and have a tubular structure; in birds and mammals, there is a greater differentiation of the cells and a well defined arrangement of the cells in the formation of the islets.

It has been well established that the pancreas is an organ which has developed from the duodenum, and in its embryologic development, the anlages first appear as buds on the duodenum. The anlages are multiple; in some animals as many as four have been found. They progress to a certain stage, independently of one another, between the folds of the primitive mesentery, to coalesce later and develop into the pancreas.

Embryology of the Pancreas in Man.—The pancreas in man develops from cells in the duodenum which differentiate and form two anlages in

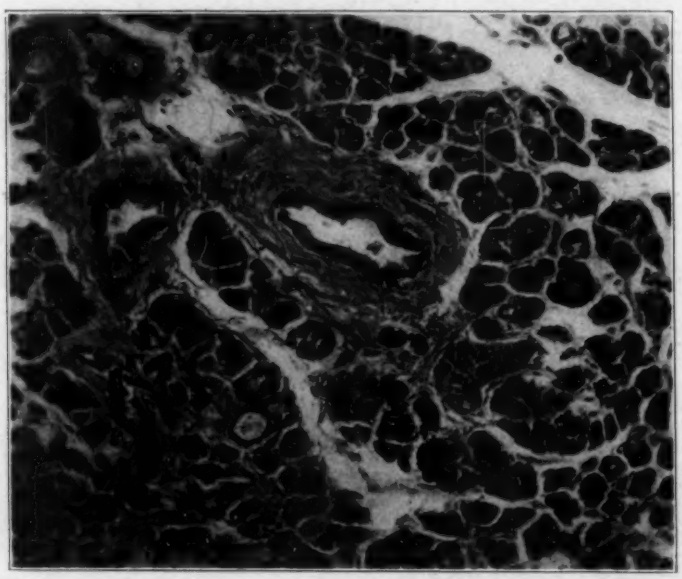

Fig. 4 (A129972).—Accessory pancreas, showing acini, ducts and islet, with increase in connective tissue.

the embryo of 3 or 4 mm. in length. The dorsal pancreatic anlage begins as an outpouching on the duodenum, the ventral pancreatic anlage as a grooved bud arising from the common bile duct at its juncture with the duodenum (Fig. 8). The growth of the dorsal pancreas is more rapid than that of the ventral. The anlages grow separately until by their circumrotation and growth around the inner aspect of the duodenum they meet posteriorly, where they coalesce and continue development in one mass in the dorsal mesentery. The body and tail grow upward and to the left so that they lie in the dorsal mesogastrium, posterior to the stomach. As the stomach and dorsal mesogastrium change position, the pancreas moves within the dorsal mesogastrium until its position is

transverse, when it becomes firmly fixed to the parietal peritoneum of the posterior abdominal wall.

The primitive outpouchings are lined with columnar epithelium similar to that in the duodenum. As the buds grow, the epithelium develops branching ducts ramifying the connective tissue. The main duct of the dorsal pancreas opens into the duodenum, while the main duct of the ventral pancreas opens into the common bile duct at the ampulla. When the dorsal and ventral anlages unite, the main duct of the ventral pancreas anastomoses laterally into the main duct of the dorsal pancreas. In this way, the main duct of the ventral pancreas with the distal half of the duct of the dorsal pancreas forms the duct of Wirsung, and the proximal half of the duct of the dorsal pancreas is the duct of San-

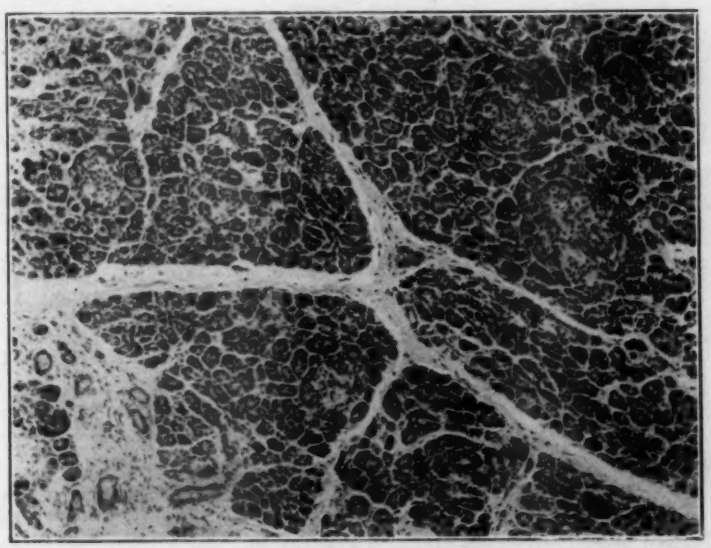

Fig. 5 (A130601).—Accessory pancreas, showing acini, small ducts and four islets.

torini. When the embryo is from 26 mm. to 33 mm. in length, and the tail of the pancreas extends well out into the dorsal mesogastrium, branching tubules can be seen throughout the gland. No acini or islets are to be seen at this stage, and there is no evidence of lobulations. The connective tissue forms the major portion of the organ. At the end of the branches of the main duct, the tubules have an enlarged bud. This bud branches and forms new tubules until the acini begin to form by several buds at the tip of each nodule. After the acini have begun to form throughout the gland, the islet cells appear in the connective tissue along the small ducts. Pearce [8] found masses of cells which he identi-

8. Pearce, R. M.: The Development of the Islands of Langerhans in the Human Embryo, Am. J. Anat. **2**:445-455, 1902-1903.

fied as islet cells in an embryo of 54 mm. The connective tissue is derived from the mesodermal tissue of the dorsal mesentery.

In a general way, it may be said that each phase of the embryologic development of the pancreas in man, from the time the cells which form the anlages begin their differentiation in the wall of the duodenum until the gland becomes fixed in its transverse position, represents a mature development in a lower vertebrate. But, in contradistinction to this, all the variations in form which occur in the lower vertebrates are not represented in man.

SURGICAL CONSIDERATIONS

The normal conditions prevailing in the area where a mass of accessory pancreatic tissue is engrafted may differ greatly from those under which the normal gland exists, and for this reason, it is logical to presuppose that in the abnormal location in which these masses of accessory pancreatic tissue are found, they are more prone to inflammatory processes and malignancy. Therefore, in addition to the surgical and pathologic conditions usually found in the normal pancreas, there may be others resulting from the abnormal situation of the accessory pancreatic tissue.

Opie [3] has pointed out in the necropsy specimens studied by him the occurrence of chronic interstitial inflammation in accessory pancreatic tissue and Mayo-Robson [9] has reported a case found at operation. Warthin [1] reported two cases in which there was increased connective tissue, and in one of these there were also areas of localized fat necrosis in the surrounding tissue. Gibson [10] reported a case which he believed to be an acute pancreatitis.

The possibility that accessory pancreatic tissue may be the cause of carcinoma has been suggested by Eloesser [11] and others, but our only conclusive evidence is from Branham,[12] who reported a case of pyloric obstruction in which he performed a pylorectomy for a mass "2 inches long and 1 inch across. This was found, on microscopic examination by Professor Welch, to be a 'malignant adenoma' of the pylorus originating in misplaced pancreatic tissue."

It is possible that carcinoma of the duodenum, which is occasionally observed, originates in accessory pancreatic tissue. Such origin, how-

9. Mayo-Robson, A. W.: A Case of Chronic Pancreatitis Probably Starting in an Accessory Pancreas, Lancet **2**:1823-1825, 1905; Anatomy of the Pancreas in Relation to Its Diseases, Brit. M. J. **1**:1153-1161, 1908.

10. Gibson, C. L.: Accessory Pancreas in the Gastro-Intestinal Tract, Med. Rec. **82**:426-427, 1912.

11. Eloesser, L.: Die in den letzten 10 Jahren an der Heidelberger chirurgischen Klinik beobachteten Fälle von Pankreaserkrankungen Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:195-294, 1908.

12. Branham, J. H.: Operative Treatment of Cancer of the Stomach, with Report of Six Partial Gastrectomies, Maryland M. J. **51**:144-148, 1908.

ever, cannot be established in any given case of carcinoma of the duodenum, as in all probability, the accessory pancreatic tissue if present will be unrecognizable. The histogenesis of carcinoma from these disconnected masses of tissue will be proved only by a careful study of a number of specimens in which all the pathologic changes can be demonstrated from the normal to a well defined carcinoma.

The tendency for intussusception in cases in which there is a tumor in the wall of the intestine has long been known. Benjamin [13] reports a case of obstruction of the intestine in which abdominal exploration revealed an intussusception of the jejunum. The intussusception was

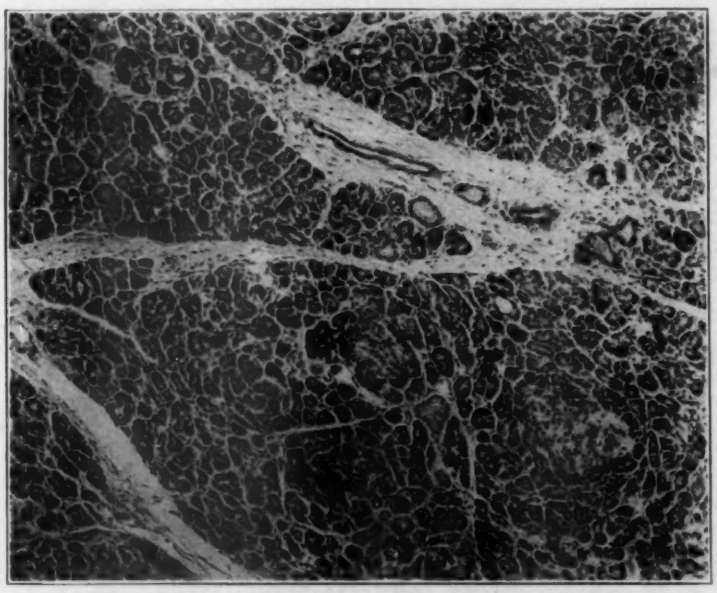

Fig. 6 (A130601).—Accessory pancreas, showing acini, ducts and two islets.

reduced and found to contain a tumor-like mass which proved to be an accessory pancreas. Several similar cases have been reported.

Diverticula of the intestinal wall with aberrant pancreatic tissue in the tip of the diverticulum have been reported by several observers who regarded the accessory pancreatic tissue as the cause of the diverticulum. In a few of these cases, the tip of the diverticulum, containing the inflammatory accessory pancreatic tissue, had become attached to the abdominal wall or to the intestine, and the band thus formed produced a loop-hole through which a coil of the small intestine passed, later to become obstructed and strangulated.

13. Benjamin, A. E.: Accessory Pancreas with Intussusception, Ann. Surg. **67**:293-298 (March) 1918.

DISCUSSION

Inasmuch as the collated studies of disconnected pancreatic tissue, recorded in the literature and supplemented by my own observation, have proved that these masses contain all the histologic units of the pancreas, that they have a blood supply, carry on a function independently of the pancreas, may become malignant, produce obstruction, intussusception and diverticula, the finding of this tissue is of more than academic interest.

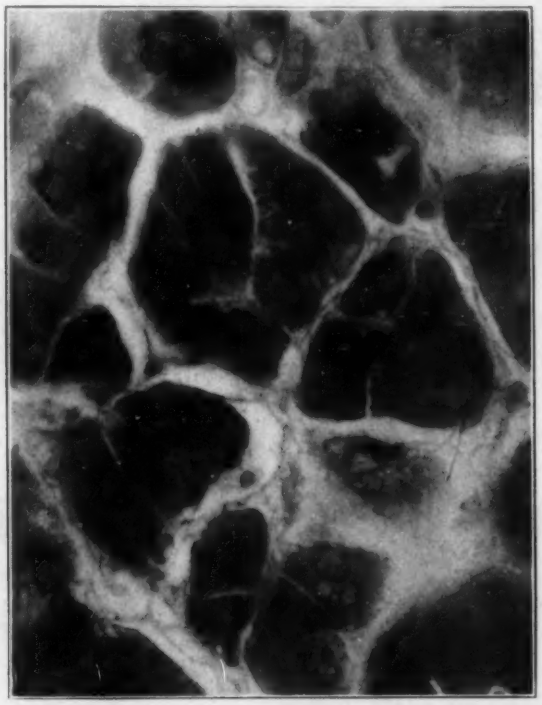

Fig. 7 (A130601).—Oil immersion photomicrograph of acini, showing large zymogen granules in the cytoplasm of the apical portion of the acinic cells.

There does not appear to be an accepted theory as to the cause of accessory pancreatic tissue. Zenker [14] believed it to be an anomaly occurring very early in embryonic life by the formation of an additional diverticulum which develops into a single gland mass independently of the normal pancreas and, as the intestine grows longer, may be carried away a great distance. Glinski [15] attributes it to a failure of one or

14. Zenker, F. A.: Nebenpankreas in der Darmwand, Virchows Arch. f. path. Anat., **21**:369-376, 1861.

15. Glinski, L. K.: Zur Kenntniss des Nebenpankreas und verwandter Zustände, Virchows Arch. f. path. Anat. **164**:132-146, 1901.

more of the primitive anlages to coalesce with the main pancreas, which he believed developed chiefly from the ventral anlage.

Warthin states, "It is more probable that accessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine either upward or downward."

Accessory pancreatic tissue cannot be looked on as an anlage which has failed to coalesce with its codeveloping companion. If it were due to failure to coalesce, the masses would be large and would be found always in the duodenum, whereas, in fact, all the aberrant masses are small and the accessory tissue has been found in the stomach, duodenum,

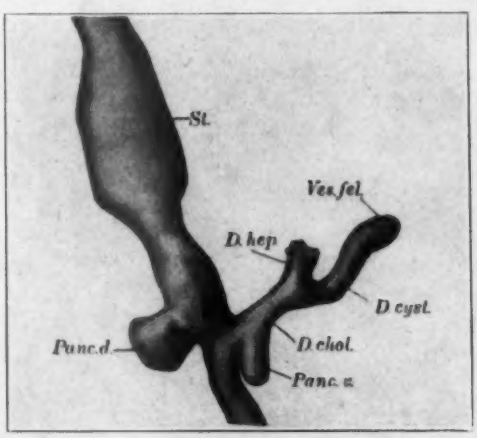

Fig. 8.—Reconstruction from a human embryo of 7.5 mm. (H.E.C. 256, Thyng, F. W.: Am. J. Anat. **7**:489-503, 1908), × 55; *D. chol.*, ductus choledochus; *D. cyst.*, ductus cysticus; *D. hep*, ductus hepaticus; *Panc. d.*, pancreas dorsale; *Panc. v.*, pancreas ventrale; *St.*, stomach; *Ves. fel.*, vesica fellea.

jejunum and ileum, spleen, splenic capsule, mesentery, omentum and umbilicus. Nor can these masses of accessory pancreatic tissue be looked on as embryonic rests. They are adult tissues composed of differentiated cells having a function similar to the normal pancreas, and do not, in any way, conform to the theory of Cohnheim.

It is obvious that any hypothesis which may be advanced will of necessity be speculative, but after a review of studies of embryos recorded in the literature and the study I have made of sections of human embryos, I believe a reasonable explanation may be made, on developmental grounds, of the pancreas, stomach, intestines and mesentery. It is true that in the early stage of the development of the intestine and pancreas these structures resemble the intestine of the adult species of some of the lower orders of vertebrates, but we should be going far

afield to theorize on atavistic tendencies of the gland in explaining this abnormality. It should be borne in mind that this gland is changing its position and growing rapidly between the layers of the primitive mesentery from the time the anlages appear until the gland becomes firmly fixed to the parietal peritoneum of the posterior abdominal wall, and, at the same time, the stomach is developing, the intestine is rapidly increasing in length and pulling with it the mesentery so that there is a movement of these tissues in directions opposed to that of the pancreas.

In man, the primitive anlage which develops into the pancreas appears when the embryo is from 3 mm. to 4 mm. in length. At this time the primitive intestine is an almost straight tube and the buds are

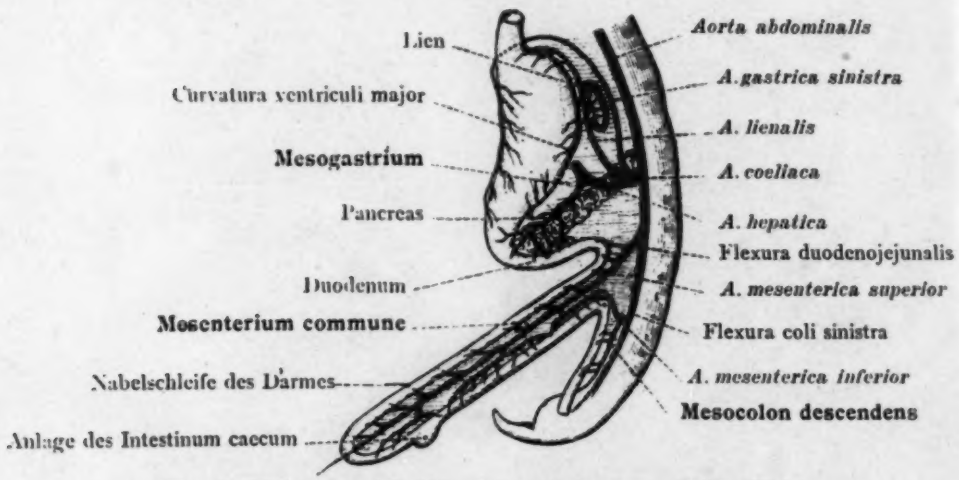

Fig. 9.—Taken from Toldt's Atlas of Anatomy 4:451, 1914.

comparatively large. The growth of the pancreas, like that of the liver, suprarenals and kidneys, is very rapid, and it attains a comparatively large size before the intestine is markedly increased in length (Fig. 9). The dorsal and ventral pancreatic anlages conjoin when they meet posterior to the duodenum, and continue to grow upward and to the left.

During the partial circumrotation of the posterior and anterior pancreatic anlages until they coalesce to form one body, and during the migration of the body upward, its branching buds come in contact with the wall of the stomach, intestine or mesentery and may become engrafted thereon. Later, as the gland pulls away in its growth and movement, the small bud which has become attached to the wall of the intestine is cut off and becomes incorporated in the wall of the intestine as a graft. As the intestine grows in length, the graft becomes further separated from the pancreas, unless the graft happens to be in the stomach or duodenum.

While the gland is growing and changing its position in the primitive mesentery, the mesentery is also growing and pulling in the opposite direction. In this manner, a bud may become attached to the mesentery and be pulled away from the gland. This may explain the case reported by Warthin in which he found an accessory pancreas in the fat of the great omentum.

TABLE 1.—ACCESSORY PANCREAS: THIRTY-TWO CASES REPORTED IN THE LITERATURE SINCE 1904

Year	Reported by	Location	Microscopic Structure
1894	Biggs[2]	Pylorus	Pancreas
1901	Gandy and Griffon[16]	Duodenum	Pancreatic acini, ducts and islets
1903	Reitmann[17]	Ileum	Pancreatic acini, ducts and islets
1903	Reitmann[17]	Jejunum	Pancreatic tissue
1904	Turner[18]	Jejunum	Pancreatic acini and ducts
1904	Bize[19]	Diverticulum of intestine	Pancreatic acini and ducts
		Diverticulum of intestine	Pancreatic acini and ducts
1904	Müller[20]	Stomach	Pancreatic acini and ducts
1904	Alburger[21]	Jejunum	Pancreatic acini and ducts
1905	Lewis[22]	Small intestine	Pancreatic acini and ducts
1905	Mayo-Robson[9]	Duodenum	Pancreatic acini
1906	Thelemann[3]	Stomach	Pancreatic acini, ducts and islets
1907	Basselt[24]	Diverticulum of duodenum	Isolated bits of pancreatic tissue
1907	Basselt[24]	Diverticulum of duodenum	Isolated bits of pancreatic tissue
1908	Branham[12]	Stomach	Malignant adenoma of pancreatic tissue
1908	Clogg[25]	Diverticulum of intestine	Pancreatic tissue
1908	Thompson[26]	Diverticulum of intestine	Pancreatic tissue
1909	Reynier and Masson[27]	Pylorus	Pancreatic acini, ducts and islets
1909	Von Heinrich[28]	Jejunum	Pancreatic acini and ducts
1910	Weidman[29]	Splenic capsule	Pancreatic acini, ducts and islets
1911	Finkelstone[30]	Jejunum	Pancreatic acini and ducts
1912	Gibson[10]	Stomach	Pancreatic acini and ducts
1913	Carwardine and Short[31]	Jejunum	Pancreatic tissue
1913	Carwardine and Short[31]	Jejunum	Pancreatic tissue
1913	Kremer[32]	Jejunum	Pancreatic acini, ducts and islets
1913	Kremer[32]	Jejunum	Pancreatic acini, ducts and islets
1913	Kremer[32]	Jejunum	Pancreatic acini and ducts
1913	Kremer[32]	Jejunum	Pancreatic acini, ducts and islets
1913	Kremer[32]	Jejunum	Pancreatic acini, ducts and islets
1913	Kremer[32]	Duodenum	Pancreatic acini, ducts and islets
1918	Benjamin[13]	Jejunum	Pancreatic acini and ducts
1919	Nieuwenheijse[33]	Stomach	Pancreatic tissue

The buds from the primitive anlage contain the germinative cells from which all the histologic units of the gland can develop. So, in case the graft finds a suitable environment and lives, it will develop into a small accessory gland with all the function of the pancreas. The size to which the accessory pancreatic tissue grows is in proportion to the normal capabilities of development of the bud which becomes engrafted in the abnormal situation, and of the environment it finds therein.

16. Pancréas surnuméraire, Bull. et mém. Soc. anat. d. Paris **76**:451-453, 1901.

17. Zwei Fälle accessorischem Pankreas, Anat. Anz. **23**:155-157, 1903.

18. An Example of Accessory Pancreas, Lancet **2**:1566, 1904.

19. Etude anatomo-clinique des pancréas accessoires situés a l'extrémité d'un diverticule intestinal, Rev. d'orthop. **5**:149-159, 1904.

20. Accessory Pancreas in Posterior Wall of Stomach, Proc. Path. Soc., Philadelphia **7**:225, 1904.

21. Aberrant Pancreas in Wall of Jejunum, Proc. Path. Soc., Philadelphia **7**:227-229, 1904.

22. Note Upon an Accessory Pancreas in the Intestinal Wall, Med. & Surg. Rep. City Hosp., Boston, 1905, p. 172.

23. Ueber accessorisches Pankreas in der Magenwand, Deutsch. Ztschr. f. Chir. **85**:692-709, 1906.

24. Duodenal Diverticula, with Especial Reference to Diverticula Associated with Pancreatic and Biliary Ducts, Tr. Chicago Path. Soc. **7**:83-94, 1906-1909.

25. Acute Intestinal Obstruction, Lancet **1**:639-640, 1908.

26. Diverticula of the Intestinal Tract, Lancet **1**:860, 1908.

27. Sténose pylorique due à un lobule pancréatique aberrant, Bull. de l'Acad. de méd. **62**:100-106, 1909.

28. Ein Beitrag zur Histologie des sogen, akzessorischen Pankreas, Virchows Arch. f. path. Anat. **198**:392-401, 1909.

29. Aberrant Pancreas in the Splenic Capsule, Proc. Path. Soc., Philadelphia **13**:267, 1910.

30. Accessory or Aberrant Pancreas, with Report of a Case, J. A. M. A. **57**:1124-1125 (Sept. 30) 1911.

31. The Surgical Significance of the Accessory Pancreas, Ann. Surg. **57**: 653-657, 1913.

32. De la fréquence des pancréas accessoires, Arch. de méd. expér. et d'anat. path. **25**:595-602, 1913.

33. Over het pancreas accessorium, Nederlandsch Tijdschr. v. Geneesk. **26**: 2105-2113, 1919.

A SHORT ACCOUNT OF THE DEATHS OCCURRING IN THE GYNECOLOGIC SERVICE OF THE JOHNS HOPKINS HOSPITAL DURING THE YEAR 1919

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In the course of a discussion of the results of the year's work, at a recent meeting of the gynecologic staff, it was suggested that we might, with profit, briefly analyze the histories of our fatal cases, inasmuch as one can often learn more from failures than from successes. At Dr. Cullen's request, I have prepared this short paper.

During the year 1919, 1,024 patients were admitted to the gynecologic service. Of this number, 793 were anesthetized. From the accompanying table, one can gather a clear idea of the number and character of the operations performed.

NUMBER AND CHARACTER OF OPERATIONS PERFORMED DURING THE YEAR 1919

Operation	Number	Operation	Number
Appendectomy	370	Exploratory laparotomy	12
Salpingectomy (double and single)	108	Nephrectomy	2
Salpingo-oophorectomy (double and single)	216	Nephrolithotomy	1
Hysterectomy	190	Nephropexy	2
Panhysterectomy	19	Cholecystostomy	14
Perineal repair	165	Repair of vesicovaginal fistula	8
Dilation and curettage	187	Hemorrhoidectomy	13
Amputation of cervix *	17	Removal of carcinoma of vulva	2
Trachelorrhaphy	3	Cauterization of cervix	10
Modified Gilliam suspension	77	Repair of complete perineal tear	8
Modified Coffey suspension	5	Lipectomy	4
Kelly round ligament suspension	1	Ureterotomy	2
Vaginal suspension	8	Suture of vesical neck	7
Ventral fixation	3	Resection of bladder	1
Miscellaneous	48	Colostomy	2
Pelvic drainage	30	Total	1560
Radical cure of hernia	25		

* Amputation of the cervix is rarely performed on patients during the child-bearing period.

From this table, it will be seen that in only two cases was the kidney suspended, whereas, in former years, from fifteen to twenty such operations were performed. A loose kidney is very common,

especially in thin individuals, but rarely gives rise to symptoms requiring operative interference. Formerly, it was deemed necessary to stitch up the kidney in those cases in which the renal discomfort was marked, but Dr. Hunner, and later, others have found that the pain in many of these cases is due to a ureteral stricture, and that after one or two ureteral dilations the discomfort disappears, and operation is rendered unnecessary.

Following out the suggestion of Dr. Kelly, made years ago, the gallbladder region is invariably palpated in every case in which there is the faintest suspicion of trouble in the right upper quadrant, just as soon as the abdomen is opened, because when a pelvic infection exists, the infection might readily be carried into the upper abdomen if the examination is deferred until the pelvic operation has been completed. It is interesting to note that among more than 400 laparotomies, in which this routine examination was made, in only fourteen cases, or about 3.5 per cent., was trouble found in the gallbladder.

REPORT OF DEATHS

Case 1 (Gyn. No. 24669).—E. M., white, aged 31, was admitted to the hospital on Jan. 18, 1919. She had been married fourteen years, but had never been pregnant. The menstruation had been irregular for the last ten years, and for the last year there had been amenorrhea. During that period, however, she had had irregular bleeding five or six times, and the abdomen had gradually increased in size, in eighteen months, to that of a full term pregnancy. She had very little pain or discomfort, but had had a temperature varying from 100 to 103 F. A diagnosis of left ovarian cyst was made, and the patient was sent home for two weeks.

She was readmitted on March 5. The leukocyte count was 5,400, and hemoglobin 42 per cent.

The uterus, tubes, ovaries and appendix were removed by Dr. Hampton in two hours and five minutes. At operation a tuberculous peritonitis was found together with a ruptured right ovarian cyst.

On the evening of the fourth day the patient suddenly became cyanotic, had great difficulty in breathing, complained of severe pain in the chest, and died in a few minutes.

The clinical diagnosis was pulmonary embolism.

Necropsy was refused.

Case 2 (Gyn. No. 24747).—S. S., colored, aged 37, was admitted on March 21, 1919. She had been married seven years, but had never been pregnant. She complained of occasional pain in the left side of the abdomen. She had a retroposition of the uterus, her hemoglobin was 65 per cent.

March 26, Dr. Wooley shortened the round ligaments according to the modified Gilliam method and removed the appendix. The operation lasted one hour.

On April 6 (the twelfth day), the patient suddenly collapsed and died in fifteen minutes.

Necropsy (No. 5869) revealed a thrombosis of the pelvic veins, pulmonary embolism with occlusion of the main branches of the pulmonary arteries of both lungs, and focal necroses in the liver.

CASE 3 (Gyn. No. 24894).—H. R., colored, aged 45, was admitted on May 9, 1919. She had an umbilical hernia which had gradually increased in size until the umbilical ring was 6 cm. in diameter. Her hemoglobin was 83 per cent., blood pressure was 204 systolic and 120 diastolic. Operation was performed, May 22, by Dr. Shaw for radical cure of the umbilical hernia. Duration of the operation was one hour and forty-five minutes.

On the tenth day she developed hesitancy of speech and the left side of the face was drawn. She went into coma at 6 p. m. and died at 7 a. m. on the following morning.

Necropsy (No. 5920) revealed a pulmonary embolus.

CASE 4 (Gyn. No. 24986).—L. G., white, age not obtained, admitted July 6, 1919, was suffering from a puerperal infection due to a criminal abortion performed nine days before. When the patient entered the hospital she was in coma and no history could be obtained. Operation was out of the question, and the patient died a few hours after admission.

The diagnosis was puerperal sepsis. This was a coroner's case.

CASE 5 (Gyn. No. 25153).—F. S., white, aged 35, admitted Sept. 3, 1919, had an inoperable squamous-cell carcinoma of the cervix. The erythrocyte count was 1,800,000, the hemoglobin 12 per cent. No operation was attempted. She died on September 9.

Necropsy (No. 5999) revealed extensive metastases to the pelvic, retroperitoneal and inguinal lymph glands. There were also cirrhosis of the liver, duodenal ulcer and pulmonary edema.

CASE 6 (Gyn. No. 26065).—M. C., colored, aged 64, was admitted July 31, 1919. The menopause had occurred twenty years before. She gave a history of vaginal bleeding for two months. The cervix was replaced by a friable cauliflower-like cancerous growth. The blood pressure was 150 systolic and 105 diastolic; hemoglobin was 70 per cent.

August 2, Dr. Hampton performed a panhysterectomy, and the tubes and ovaries were also removed. The duration of the operation was two hours. The patient did not recover consciousness, and died thirty-six hours after cancerous operation.

Necropsy (No. 5968) revealed double bronchopneumonia.

CASE 7 (Gyn. No. 25014).—M. P. W., white, aged 45, admitted July 2, 1919, had marked diastasis of the recti and an enormous accumulation of fat in the abdominal wall. She weighed 194 pounds.

July 5, Dr. Shaw performed a lipectomy and brought the rectus muscles together. The operation required one hour.

On the fifteenth day, the first day the patient was up, she suddenly became cyanotic, her respirations were labored, and she died fifteen minutes after the onset of the symptoms.

The diagnosis was pulmonary embolism.

Necropsy was refused.

CASE 8 (Gyn. No. 25194).—A. G., white, aged 36, admitted Sept. 13, 1919, had become infected as the result of a criminal abortion. Her temperature was 104 F., leukocyte count 11,000, and hemoglobin 79 per cent. A blood culture showed *Streptococcus hemolyticus*.

Dr. Brady, on September 15, removed the infected placenta. The patient died on September 26. As this was a coroner's case, no necropsy was performed.

CASE 9 (Gyn. No. 25249).—A. T., white, aged 39, was admitted on Sept. 26, 1919. The patient had been operated on in a Detroit hospital three years before. The uterus, tubes, and ovaries were removed. At that time the rectum was injured and a rectal stricture developed. She was admitted on the surgical service of this hospital and the stricture was dilated. A general peritonitis followed. She was transferred to the gynecologic department for vaginal drainage. Her general condition did not improve. She died on October 13.

Necropsy was refused.

CASE 10 (Gyn. No. 25390).—M. L., white, aged 51, admitted, Oct. 27, 1919, had had backache, swelling of the ankles, and dyspnea for four years. Filling the pelvis and extending 5 cm. above the umbilicus was a large myoma. The leukocyte count was 4,400, the hemoglobin 25 per cent. The patient was transfused, and before operation the hemoglobin had risen to 40 per cent.

November 10, Dr. Cullen removed the myomatous uterus; the tubes and ovaries were also removed. The operation was a very difficult one, and a large amount of blood was lost. The hemoglobin two days later was 30 per cent.

The patient did well until the eleventh day, when she developed phlebitis of the left femoral vein. On Nov. 22, 1919, she suddenly collapsed. Her respirations grew shallow and ceased. Death was evidently due to pulmonary embolism.

Necropsy was refused.

CASE 11 (Gyn. No. 25450).—D. C., colored, aged 38, was admitted Nov. 10, 1919. In 1906, the patient was on the surgical service of the Johns Hopkins Hospital. Her gallbladder was drained and a stone removed from the common duct.

In 1915 she again entered the Johns Hopkins Hospital. At that time the gallbladder was removed and an appendectomy was performed. Prior to closing the abdomen, the operator examined the right kidney and found that it was large and contained a stone. Three months later she entered the gynecologic service. The phenolsulphonephthalein output at that time was 24 per cent. in the first hour. Two stones were removed from the right kidney.

One week before her admission in 1919, she had pain in the right kidney region with the formation of a painful tumor, 10 cm. in diameter at this point. The leukocyte count was 13,000; the hemoglobin was 45 per cent. The phenolsulphonephthalein output in two hours was nil, the urine was very foul and loaded with pus. The right ureter was catheterized and pure pus was obtained. Cultures from this yielded the colon bacillus. The roentgen-ray examination demonstrated large stones in both kidneys.

Operation was performed, November 22, by Dr. Shaw. Under local anesthesia with 0.25 per cent. procain, a right perinephritic abscess was incised and drained, and 500 c.c. of pus were obtained.

The patient was transfused on November 26, 500 c.c. of citrated blood being introduced. Uremia gradually developed and the patient died on December 8, sixteen days after the palliative operation.

Necropsy (No. 6079) revealed bilateral pyonephrosis and bilateral nephrolithiasis.

CASE 12 (Gyn. No. 25514).—A. J., white, boy, aged 2 days, was admitted, Dec. 29, 1919, with an imperforate anus. Operation was performed, December 29, by Dr. Cullen. As the rectum could not be located on perineal section, a temporary colostomy was performed. Death occurred thirty hours later.

Necropsy (No. 6108) revealed bilateral hydronephrosis. Both kidneys were in the pelvis. The ureters for the lower 4 cm. were impervious. The rectum was lacking. It would have been impossible for this child to live.

CASE 13 (Gyn. No. 25345).—M. H., white, aged 38, was admitted Nov. 10, 1919. The patient had been married six years and had never been pregnant. One brother had died of tuberculosis. For the last seven weeks she had noticed a gradually increasing abdominal tumor and during this time she had lost 25 pounds. She had had a rather obstinate constipation.

On examination we found an abdominal tumor, quite hard, irregular in outline, fairly movable, arising from the pelvis and extending 3 cm. above the umbilicus. It was thought to be a myoma.

On November 11 an exploratory laparotomy was performed by Dr. Cullen, but the loops of the bowels were everywhere so densely adherent to one another that it was impossible to reach the pelvic organs. Any attempt to free the adhesions would have been futile. The patient died six hours later.

Necropsy (No. 6049) revealed a tuberculous peritonitis, although no tubercles were to be seen at operation, even after very careful inspection.

CASE 14 (Gyn. No. 25505.)—A. S., white, aged 64, admitted Nov. 20, 1919, had had bloody urine for four years. Her hemoglobin was 46 per cent.; the leukocyte count was 14,000. The patient had a large papillomatous mass in the base of the bladder. It was about 6 cm. in diameter and occluded the left ureteral orifice. Microscopic examination of the tumor disclosed carcinoma.

No operation was performed, but radium was tried. The tumor, however, rapidly increased in size and became firmly fixed in the left pelvic wall. She died on December 26.

Necropsy was refused.

COMMENT

From the foregoing case reports, it will be noted that in a total number of 1,024 cases there were fourteen deaths. These deaths may be best analyzed by groups.

In three of the cases no operation was performed.

In Case 4 (Gyn. No. 24986), we had to deal with an infected criminal abortion. The woman was in a comatose condition when she entered the hospital and died very soon.

In Case 5 (Gyn. No. 25153), there was an inoperable carcinoma of the cervix, and in Case 14 (Gyn. No. 25505) an inoperable carcinoma of the bladder.

Group 1: Cases 12, 8, 9, 11 and 13 were desperate surgical risks. In Case 12 (Gyn. No. 25514), the child was only 2 days old, and had an imperforate anus. A colostomy was performed, and the child speedily succumbed. Necropsy showed that the ureters were impervious in their lower ends, and that as a consequence the pelves of both kidneys were dilated. No operation would have saved the child.

In Case 8 (Gyn. No. 25194), we had an infected criminal abortion with a temperature of 104 F. Nothing was done except to remove the infected placenta. Blood cultures showed *Streptococcus hemolyticus*.

In Case 9 (Gyn. No. 25249), the patient was referred from the surgical service with a general peritonitis following rupture of a rectal stricture. This patient was so ill on admission that nothing but vaginal drainage was attempted.

In Case 11 (Gyn. No. 25450), the patient was in a desperate condition and had practically no phenolsulphonephthalein output in two hours. Under local anesthesia, a right perinephritic abscess was opened, but uremia gradually developed and the patient died. The outlook in this case was practically hopeless.

In Case 13 (Gyn. No. 25345), an exploratory abdominal operation was performed. The intestinal loops were everywhere densely adherent, so much so, that the pelvic structures could not be located and the operation had to be abandoned. Necropsy showed a widespread peritoneal tuberculosis.

Group 2: In the following three cases, operation offered a reasonable chance of success.

In Case 1 (Gyn. No. 24669), the patient had a tuberculous peritonitis and a right-sided ovarian cyst. On the fourth day she suddenly became cyanotic, complained of severe pain in the chest, and died a few minutes later. The symptoms indicated pulmonary embolism.

In Case 6 (Gyn. No. 26065), the woman underwent an extensive operation for carcinoma of the cervix. She did not recover consciousness, and died thirty-six hours after operation. Necropsy revealed double bronchopneumonia.

In Case 10 (Gyn. No. 25390), the patient had a large myoma. On admission the hemoglobin was 25 per cent. After transfusion, it rose to 40 per cent. On the eleventh day after hysterectomy she had a phlebitis and on the twelfth day she suddenly collapsed and died with signs of pulmonary embolism.

Group 3: Three unexpected deaths occurred in cases in which the operations had been simple.

In Case 2 (Gyn. No. 24747), the patient entered the hospital on account of a retroposition. The round ligaments were shortened by the modified Gilliam method and the appendix was removed. She did well until the twelfth day when she suddenly collapsed and died in fifteen minutes. At necropsy thrombosis of the pelvic veins was found. There were pulmonary emboli with occlusion of the main branches of the pulmonary arteries in both lungs. Focal necroses were also found in the liver.

In Case 3 (Gyn. No. 24894), the patient had a large umbilical hernia, and a rather high blood pressure. On the tenth day after operation she developed a hesitancy of speech. The left side of the face was drawn. She went into coma the same evening and died the next morning. Necropsy disclosed a pulmonary embolus.

In Case 7 (Gyn. No. 25014), the patient had a great quantity of abdominal fat, also marked diastasis of the rectus muscles. A lipectomy was performed and the rectus muscles were approximated. On the fifteenth day, the first day that she was up, she suddenly became cyanotic and her respirations grew labored. She became unconscious, and died fifteen minutes after the onset of the attack. The symptoms were those of pulmonary embolism. A necropsy was refused.

The deaths in these three cases were undoubtedly due to thrombosis of the veins followed by the escape of emboli to the lungs.

CONCLUSIONS

The statistics recently published by Wharton and Hampton from this clinic clearly indicate that trauma of the large veins at operation is an important factor in the causation of thrombi, and Dr. Cullen in the operating room has been insistent that great care be taken not to injure the small veins beneath the rectus muscles. Simple traction on the under surface of the muscle with the finger when the abdomen is being opened will tear them, and troublesome oozing may follow. These veins should be promptly tied and any clotted blood removed. Dr. Cullen believes that the lack of this simple precaution is in some cases responsible for subsequent thrombosis of the pelvic veins.

With the increasing use of transfusion when the hemoglobin is low, and with the more delicate handling of the tissues, the operative mortality will be still further reduced, but even then a sudden fatality from an embolus will occasionally startle us and make us realize that we are not infallible and that we still have much to learn in the handling of abdominal cases.

It is the intention of the gynecologic department to publish a short account of the deaths occurring each year.

DIVERTICULUM OF THE FIRST PORTION OF THE DUODENUM *

ERNEST K. CULLEN, M.D.

DETROIT

The literature on diverticula of the duodenum has been so fully considered by Cole and Roberts [1] and by Case,[2] that I shall, without further comment, add this case to the list of those already reported.

REPCRT OF CASE

History.—W. B., aged 40, married, was referred by Dr. William H. Weir of Cleveland, March 30, 1917, complaining of some discomfort in the right lower abdominal quadrant with associated nervousness and severe headaches. She had one child, 6 years old. In 1913, dilation, curettage and trachelorrhaphy were performed. A slight decensus of the uterus being present, a Smith-Hodge pessary was inserted.

Physical Examination.—The patient's general physical condition was good. There was some tenderness elicited on deep palpation over McBurney's point. There was slight decensus of the uterus. Examination of the eyes was negative. The urine was normal.

Treatment and Course.—Tonic treatment was prescribed and the patient soon showed marked improvement.

On May 26, 1920, the patient again consulted me. She stated that with the exception of some trouble with carious teeth one year before, her health had been good until eight weeks before this consultation. At that time she had an acute attack of "gastro-intestinal grip," and consulted my colleague, Dr. S. C. Hanna.

The onset of this attack was marked by severe vomiting, a rise of temperature to 102 F. and severe diffuse pain over the epigastric and gallbladder regions. There was no jaundice, but there was obstinate constipation. The pain which had persisted with some intermittence had assumed a boring-like character, most pronounced from three to four hours after meals, and was located just to the right of the median line. On light palpation, considerable tenderness was elicited, but no definite spasm was present. There was also tenderness to a less degree over the gallbladder area. The area of stomach tympany was not increased. There was very slight tenderness on deep palpation over McBurney's point.

The patient was referred to Drs. P. M. Hickey and William A. Evans for roentgenologic examination. Their report follows:

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* Read before the Thirty-Third Annual Session of the Southern Surgical Association, Hot Springs, Va., December, 1920.

1. Cole, L. G., and Roberts, D.: Diverticula of the Duodenum, Surg., Gynec. & Obst. **31**:376 (Oct.) 1920.

2. Case, J. T.: Diverticula of Small Intestine Other Than Meckel's Diverticulum, J. A. M. A. **75**:1463 (Nov. 27) 1920.

Roentgenologic Report.—Survey of the chest shows the right and left lung fields clear, and the heart slightly enlarged. There is no disturbance of the mediastinal shadows. The stomach is of the extreme vertical type, shows good tone, the walls remaining strictly parallel during the examination. We are unable to fill the duodenal bulb by manipulation, with the patient in the erect position. Good single wave peristalsis starts at once on the ingestion of the meal. There is no evidence of an incisure.

Patient Examined Prone: The stomach is seen to be considerably dilated. There is marked two-cycle type of peristalsis, the waves being very deep and conspicuous. At times the duodenal bulb seems gigantic in its appearance,

Fig. 1.—Serial roentgenograms taken immediately following the ingestion of the barium meal, showing a large duodenal cap with some irregularity on its external aspect. Extending outward from this is the mass of barium (*A*), which represents the well defined diverticulum.

perfectly smooth, without evidence of distortion. The type of peristalsis, when considered in connection with the apparently normal bulb, would signify extragastric irritation. Serial plates will be made.

Survey at Five Hours: There is no evidence of a gastric retention. There is marked evidence of gaseous distention of the stomach and cecum. The barium is visualized in the ileum and is just beginning to fill the cecum.

Survey at Twenty-Four Hours: There is retention of the barium in a low, deformed cecum. The cecum is too low to permit of manipulation. The patient, however, refers her symptoms to the upper right quadrant. In this region

there is a mass of barium about the size of a hickory nut which seems to be sensitive to manipulation. At least, the area about this shadow is sensitive to pressure. Irregular outlining and relations of the colon are noted.

Examination at Forty-Eight Hours: There is still retention in the cecum. The cecum is elevated somewhat more than at the twenty-four hour survey. The transverse colon is ptotic, but can be elevated. The shadow noted above

Fig. 2.—Roentgenogram taken twenty-four hours after ingestion of the barium meal, still showing retention in the diverticulum (*A*).

the colon in the upper right quadrant at twenty-four hours is still present. The mass is smaller and still sensitive to manipulation.

Plates of the urinary tract show no evidence of calculus. There is lumbarization of the first sacral segment, but there is no evidence that this has any clinical significance.

Serial plates (Fig. 1) made following the ingestion of the meal show the stomach in active peristalsis, without gastric defect. There is a large duodenal cap. This shows a little irregularity on the external aspect. There is a mass of barium extending out from the outer aspect of the duodenum, which seems to push farther to the right the second portion of the duodenum, without causing duodenal stasis. *The appearance is that of a diverticulum of the duodenum.*

A plate made at twenty-four hours (Fig. 2) shows the position of the cecum and the cecal stasis as described in the fluoroscopic findings. There is a mass of barium opposite the transverse process of the fourth lumbar segment on the right side. This was the mass which was described in the fluoroscopic notes and which was sensitive to manipulation.

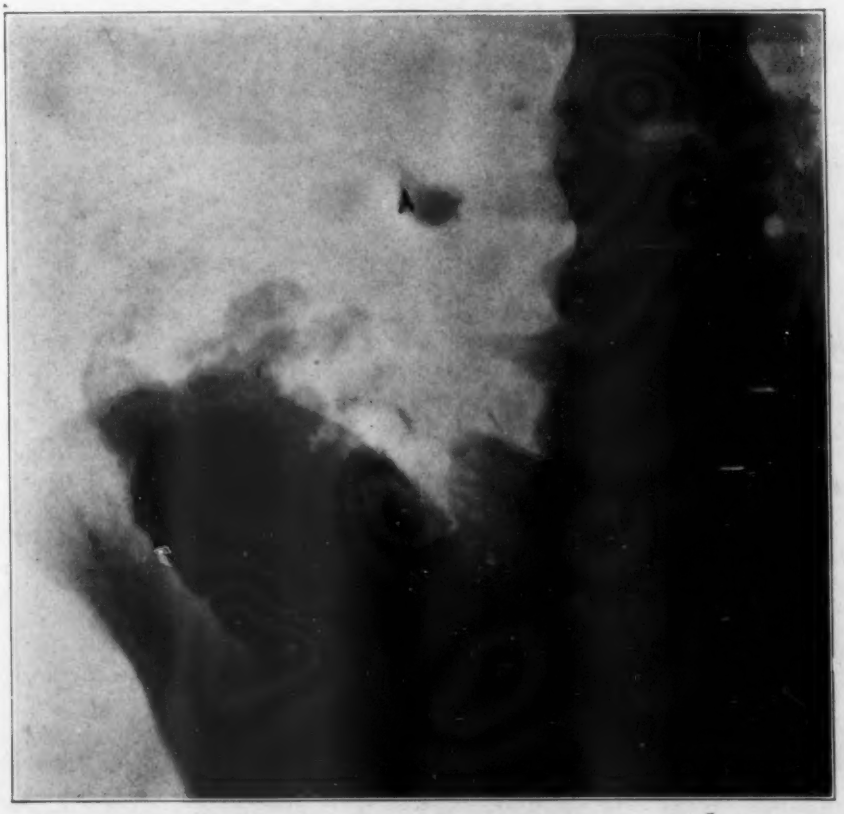

Fig. 3.—Roentgenogram taken forty-eight hours after ingestion of the barium meal, still showing retention in the diverticulum (*A*).

A plate at forty-eight hours (Fig. 3) shows still the small mass of barium opposite the transverse process of the fourth lumbar segment on the right side. The cecum is emptying somewhat, and shows elevation. No doubt the shadow described on the twenty-four and forty-eight hour plates as lying opposite the fourth lumbar segment represents the shadow which was interpreted in the serial plates immediately following the ingestion of the meal as a diverticulum of the duodenum.

Conclusion: Duodenal diverticulum, disturbance in the position, outline and function of the cecum, probably secondary to adhesions.[3]

Operation.—The upper abdomen was opened through a right rectus incision. The stomach walls were found to be normal and the pyloric orifice unobstructed. The gallbladder, duodenum and gastrocolic omentum were involved in adhesions, but the gallbladder wall was not thickened nor were stones present. It was found that a small portion of the gastrocolic omentum had in turn become adherent to the anterior portion of the duodenum and the gallbladder. In separating the adhesions, the first portion of the duodenum was pulled upward, causing a distinct sacculation. After separation of the adhesions had been completed, the first portion of the duodenum was found to be considerably redundant. There was no evidence of duodenul ulcer or other diverticula.

Consideration of the patient's symptoms, the undoubted damage to the duodenal mucosa by the retention of food in the diverticulum and the possibility of adhesions' reforming, convinced me that the performing of a gastro-enterostomy would be the safest procedure. A posterior gastro-enterostomy was then performed. The appendix, which was atrophic, was not removed. Apart from discomfort resulting from infection of the abdominal incision, convalescence was uneventful.

Roentgenologic Examination.—This was made on Oct. 13, 1920, and the report follows.

Examination at 11 a. m.: The first portion of the barium to reach the stomach passed rather quickly out through the posterior gastro-enterostomy opening. The opening appeared to be in the middle third. We attempted to force the barium up into the duodenum, but at no time was this structure outlined. After a delay of ten minutes, and in several positions, there was still no duodenal filling. The gastric evacuation by way of the new opening was slow.

Examination at 1:45 p. m.: At least 80 per cent. of the barium meal had escaped from the stomach. There was no evidence that the barium was leaving by the normal route. The duodenum and cap were not well filled.

Examination at 4 p. m.: The stomach was practically empty, with apparent filling of the duodenal cap. The escaped barium had, in part, entered the large bowel.

A plate of the upper right quadrant at four hours following the ingestion of the meal showed outlining of the duodenal cap. There was evidence of a small amount of barium in the second portion of the duodenum.

Examination at Twenty-Two Hours: No barium was detected in the upper right quadrant.

Result.—A report from the patient on Dec. 1, 1920, states that she has been on an unlimited diet for several weeks, and is free from any epigastric pain or distress.

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3. Following the ingestion of the barium meal, the pain was exaggerated, and the patient suffered considerable discomfort for seventy-two hours. A limited diet was prescribed, but little relief was experienced.

THE EFFECT ON THE KIDNEY OF VARIOUS SURGICAL PROCEDURES ON THE BLOOD SUPPLY, CAPSULE, AND ON THE URETERS *

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This experimental study of the kidney and ureter was undertaken to determine the effect produced on them by some of the common surgical procedures or by accidents to them during operations on other organs.

The problems studied have been classified into four series, and the phases investigated have been arranged in groups.

SERIES I.—The effect on the kidney and ureter of complete sudden occlusion of the ureter or of complete sudden occlusion of the ureter and the collateral venous circulation.

Group 1. Double ligation and section of the ureter (twenty-two experiments).

Group 2. Double ligation and section of one ureter and the collateral venous circulation (thirty-one experiments).

SERIES II.—The effect of occlusion of the various vascular radicals of the kidney.

Group 1. Ligation of the renal artery (five experiments).

Group 2. Ligation of one or more branches of the renal artery (sixteen experiments).

Group 3. Ligation of the renal vein (eight experiments).

Group 4. Ligation of one of the larger branches of the renal vein (two experiments).

SERIES III.—The effect on the kidney and ureter of trauma to the ureter.

Group 1. Clamping of the ureter (eleven experiments).

Group 2. Stripping of the ureter (six experiments).

Group 3. Anastomosis of the ureters (twenty-two experiments).

SERIES IV.—The effect of decapsulation of the kidney.

Group 1. Decapsulation of the kidney and wrapping it in omentum (thirteen experiments).

Group 2. Decapsulation of the kidney and wrapping it in omentum after ligation of the renal artery or branches of the renal artery (seven experiments).

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* From the Section on Surgery, Mayo Clinic.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, May, 1920.

METHOD OF EXPERIMENTATION

Dogs were used in all the experiments because of the similarity of the anatomy, and particularly of the physiology and blood supply to those of man. Each surgical procedure was carried out with the strictest observance of aseptic technic identical with that used on man. The dogs were anesthetized with ether, the abdomen shaved, and thoroughly cleansed with alcohol and benzin and two applications of 10 per cent. iodin. A straight upper right rectus incision was made in order to permit abdominal exploration and transperitoneal exploration of both kidneys and ureters. In many instances surgical procedures other than those on the kidney and ureter, such as gastro-enterostomy, partial resection of the stomach, cholecystectomy, fat transplantations, and so forth, were carried out in the study of other problems, but in no instance was a procedure undertaken which would influence the results of the problem at hand. The technic of the various surgical procedures is discussed briefly under each series of experiments. The peritoneum and fascia were closed with catgut and the skin with linen. The wound was sealed with collodion. The dogs were kept under the most favorable conditions for health.

SERIES I.—THE EFFECT ON THE KIDNEY AND URETER OF COMPLETE SUDDEN OCCLUSION OF THE URETER OR COMPLETE SUDDEN OCCLUSION OF THE URETER AND THE COLLATERAL VENOUS CIRCULATION

The first problem investigated was the effect produced on the kidney by sudden complete occlusion of the ureter and the factors concerned in the end-results. This problem has a practical significance as it is frequently necessary to ligate one of the ureters during the course of various surgical procedures on man, such as the removal of a malignant growth of the bladder or pelvis when it is impossible or does not seem advisable to make other disposition of the ureter. The ureter has been ligated almost with impunity in man although many textbooks of surgery differ as to the effect produced on the kidney.

Watson and Cunningham [1] state that complete total obstruction of the ureter does not cause hydronephrosis. Morris [2] states that sudden complete stoppage of the outflow of urine leads to rapid atrophy and ultimate disappearance of the affected kidney. Keyes [3] states that sud-

1. Watson, F. C., and Cunningham, J. H.: Diseases and Surgery of the Genito-Urinary System, Philadelphia, Lea and Febiger **2**: 1909.

2. Morris, H.: Surgical Diseases of the Kidney and Ureter, London, Cassell and Company, 1901 **2**:277.

3. Keyes, E. L.: Diseases of the Genito-Urinary Organs, New York, D. Appleton & Co., 1911, p. 852.

den complete obstruction of the ureter causes damming back of the urine on the kidney with acute renal congestion and a diminished secretion of the urine, and that this causes an increased intrarenal pressure. The congestion is exchanged for atrophy. Adami and Nicholls [4] state that complete obstruction to the outflow of urine leads to atrophy of the affected kidney.

Group 1. Double Ligation and Section of the Ureter (Twenty-Two Experiments).—In this group of experiments the operative procedure was practically the same. The appearance and relative size of the kidneys and ureters were determined by transperitoneal exploration; the intestines were packed off and the lower third of the ureters exposed. If one ureter was normal it was doubly ligated with linen and sectioned, then replaced behind the peritoneum (eighteen experiments). In two experiments the ureter was doubly ligated with catgut and sectioned. In two the ureter was ligated with catgut but not sectioned in order to demonstrate the necessity of using permanent suture material to tie off the ureter when complete occlusion is desired. The animals recovered from operation immediately, and their general health during the experiments was good. Eleven of the dogs were killed at desired intervals; five of the remaining nine died of distemper, two of sepsis from other operative procedures, and two as a result of accident. A complete necropsy was made on each animal (Table 1 and Figs. 1 to 8).

The primary effect on the kidney, resulting from ligation of the ureter, is shown in Experiment 20. There was a marked congestion and edema from the increased intrarenal pressure which partially obstructed the venous return by compression of the smaller capillaries. This pressure was at its maximum in about twenty-four hours and gradually decreased with the duration of the obstruction. Rosow [5] found an intrarenal pressure of 90 mm. in twenty-four hours, and of 6 mm. at the end of 279 days. The increased pressure soon produced a dilatation of the pelvis and ureter. The sequence of events was very regular but not uniform in all the animals with the same duration of obstruction.

The increased intrarenal pressure produced by obstruction to the outflow of urine next caused a dilatation of the pelvis of the kidney, a flattening of the renal papillae, and compression of the medulla. This process was well marked in seventy-two hours (Fig. 1). It was progressive and fairly uniform in the sequence with which the portions of the kidney were affected. First there was a definite thinning of the

4. Adami, J. G., and Nicholls, A. G.: The Principles of Pathology, Philadelphia, Lea and Febiger, 1909 **2**:770.

5. Rosow, N.: Harnleiterdruck bei Hydronephrose, Ztschr. f. Biol. **54**: 269-285, 1910.

renal parenchyma in the lateral portions of the kidney within ten days. The poles were next involved, showing a rather marked change in from fourteen to eighteen days. The median sagittal portion was the most resistant, and at twenty-one days considerable renal parenchyma remained (Figs. 2 and 3), while at four weeks or more only a very thin layer of renal parenchyma in scattered patches lining the sac remained. The interior of the kidney was partitioned off by columns of fibrous

TABLE 1.—SERIES I: THE EFFECT ON THE KIDNEY AND URETER OF COMPLETE SUDDEN OCCLUSION OF THE URETER OR OF THE COLLATERAL VENOUS CIRCULATION

Group 1: Double Ligation and Section of the Ureter (Twenty-Two Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ureter Ligated	Necropsy	Pyonephrosis	Hydronephrosis	Dilatation of Capsular Veins	Condition of Kidney not Operated On	Reoperation: Contents of Sac Removed	Sac Refilled
1 (723)	B678	12/23/16	447	Right	121	..	Large	+	Hypertrophic		
2 (506)	C 95	8/10/17	217	Right	119	..	Large	+	Hypertrophic		
3 (43)	B732	1/20/17	153	Right	386	..	Large	+	Normal		
4 (290)	B901	3/26/17	102	Right	407	..	Large	+	Normal		
5 (724)	B655	12/23/16	47	Right	54	..	Large	+	Normal		
6 (727)	B679	12/23/16	40	Right	38	..	Large	+	Hypertrophic	1/12/17	+
7 (31)	B720	1/ 3/17	28	Left	62	..	Large	+	Normal	1/17/18	+
8 (97)	B767	2/10/17	20	Left	105	..	Large	+	Normal	2/17/17	+
9 (631)	C136	9/10/17	16	Plain catgut, right	530	+	Moderate	+	Normal		
10 (17)	B706	1/ 9/17	13	Left	16	..	Moderate	+	Normal		
11 (436)	C 12	6/ 4/17	12	Right	377	..	Moderate	+	Normal		
12 (592)	C115	8/24/17	11	Plain catgut, right	506	..	Moderate	+	Normal		
13 (51)	B740	1/27/17	10	Left	50	..	Moderate	+	Hypertrophic		
14 (18)	B707	1/ 9/17	9	Left	15	..	Moderate	+	Normal		
15 (14)	B703	1/ 6/17	7	Left	13	..	Small	+	Normal		
16 (442)	C 18	6/ 8/17	6	Right	370	..	Small	+	Hypertrophic		
17 (619)	C129	8/31/17	4	Right	511	..	Dilatation of pelvis and ureter	+	Normal		
18 (725)	B528	12/23/16	3	Right	577	..		+	Normal		
19 (284)	B872	3/17/17	3	Left	154	..		+	Normal		
20 (726)	B600	12/23/16	1	Right	576	..	Congestion and edema of entire kidney	+	Normal†		
21*(252)	B874	3/17/17	223	Plain catgut, left	49	..	Ureter, normal	..	Normal†		
22*(250)	B873	3/17/17	239	Left	48	..	Ureter, partially constricted, slight atrophy of kidney		Normal		

* Ligation without section.
† Kidney operated on normal also.

tissue radiating in a fanlike arrangement from the ureteral outlet (Fig. 4). These bands or columns contained the blood vessels which with their fibrous sheaths were relatively unaffected by the intrarenal pressure that caused atrophy of the renal parenchyma lying between them. These bands of fibrous tissue caused the lobulated appearance of the surface of the kidney. The renal vessels could be seen running through the lobular grooves.

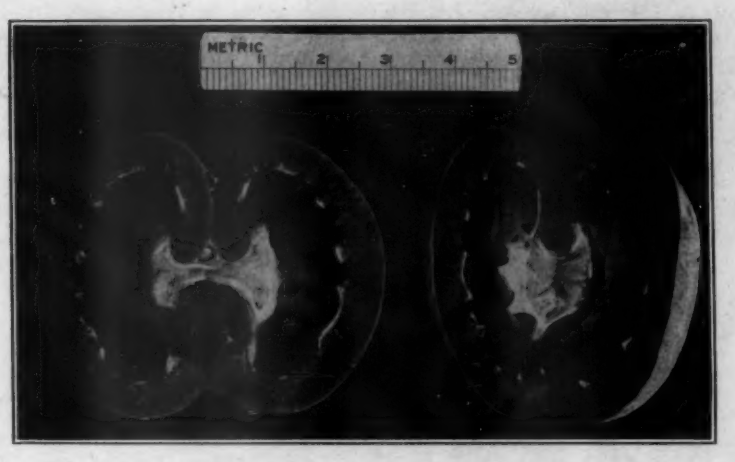

Fig. 1 (Series I, Group 1, Experiment 18 [B 528]).—Ligation of the ureter, three days' duration; beginning hydronephrosis, flattening of the renal papillae with depression and narrowing of the medulla.

Fig. 2 (Series I, Group 1, Experiment 8 [B 767]).—Ligation of the ureter, twenty days' duration; hydronephrosis; marked dilatation of the capsular vessels over the surface of the hydronephrotic sac.

Fig. 3 (Series I, Group 1, Experiment 8 [B 767]).—Marked dilatation of the renal tubules and degeneration of the renal parenchyma of kidney shown in Figure 2.

Fig. 4 (Series I, Group 1, Experiment 7 [B 720]).—Ligation of the ureter, twenty-eight days' duration; hydronephrosis; marked destruction of the renal parenchyma in the lateral portions, considerable tissue remaining in the median sagittal portion.

The pelvis and ureter were markedly dilated and the capsular veins, radiating from the pelvis and passing over the surface of the sac, were simularly dilated. The degree of dilatation of these veins seemed to depend on the amount of hydronephrosis. The changes in the renal parenchyma followed the same progressive course as the gross changes. The entire tubule (most marked in the collecting tubule and Bowman's capsule) was dilated, and the convoluted tubule and the loop of Henle were compressed. Atrophy was noted first in the convoluted tubules, but was soon followed by the same process in all the tubular structures. The glomerular tufts, like the larger blood vessels in the medulla, were much more resistant than the renal parenchyma and remained for a long time after the tubular structure had disappeared (Figs. 6 and 7).

In Experiment 6 a kidney which had been obstructed for twenty-one days had the power to secrete urine. The dog was reoperated on the twenty-first day, and the contents of the hydronephrotic sac removed. The sac was found refilled with fluid when the dog was killed on the fortieth day. In Experiments 7 and 8 the hydronephrotic sacs were evacuated on the fourteenth and seventh days, respectively, after the ureteral ligation. The sacs had refilled when the dogs were killed on the twenty-eighth and twentieth days, respectively.

The contents of the hydronephrotic sacs were acid in reaction with a fairly constant specific gravity, ranging from 1.008 to 1.010. The fluid contained albumin and urea, and usually sediment containing blood, probably the result of the early congestion of the kidney. In one experiment at necropsy a marked infection (pyonephrosis) was present.

In Experiments 1 and 12 the ureters were ligated with No. 1 plain catgut. In Experiment 1 the dog died on the sixteenth day of peritonitis from leakage of the ureter; a pyonephrosis had developed in the kidney (Fig. 8). In Experiment 12 the dog was killed the eleventh day. The capsular veins were dilated and the ureter and pelvis enlarged but collapsed, showing evidence of a previous hydronephrosis. The contents of the sac had leaked out through the ureter. In both of these experiments the catgut ligature had been absorbed with leakage of the contents of the hydronephrotic sac. In Experiments 21 and 22, the ureters were ligated with No. 1 plain catgut but not sectioned. In Experiment 21, the dog died 223 days after operation. On examination of the ureter the site of the catgut ligature could not be found. There was no dilatation of the ureter and the kidney was normal. In Experiment 22 the dog was killed in 239 days because of an infection resulting from another operation. When the ureter was examined a slight constriction was found at the point of ligation, with some dilata-

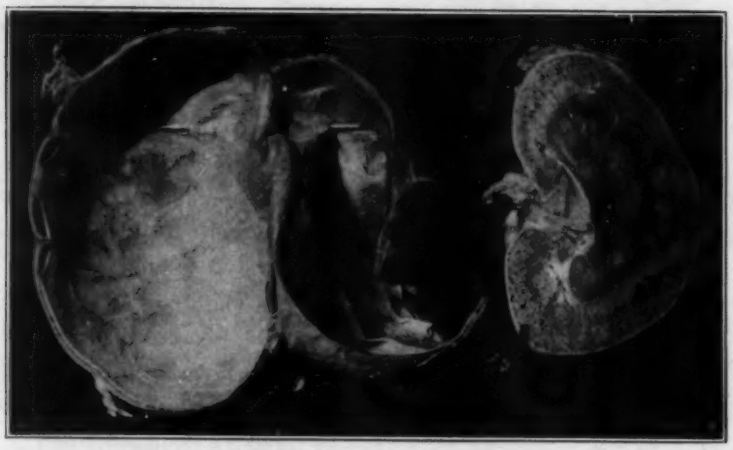

Fig. 5 (Series I, Group 1, Experiment 4 [B 901]).—Ligation of the ureter, 102 days' duration; complete destruction of the renal parenchyma; large monolocular hydronephrotic sac.

Fig. 6 (Series I, Group 1, Experiment 3 [B 732]).—Ligation of the ureter, 153 days' duration; complete destruction of the renal parenchyma; connective tissue bands radiating from the pelvis.

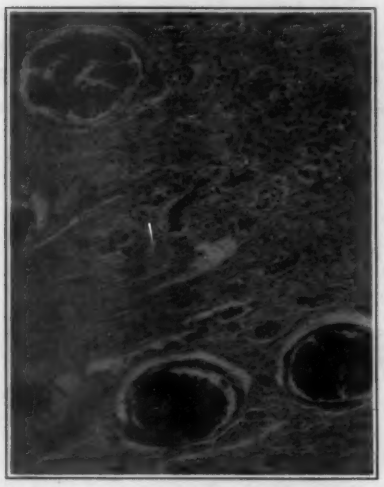

Fig. 7 (Series I, Group 1, Experiment 3 [B 732]).—Marked atrophy of the renal parenchyma of kidney shown in Figure 6; glomeruli fairly well preserved.

Fig. 8 (Series I, Group 1, Experiment 1 [B 676]).—Ligation of the ureter, 447 days' duration; enormous lobulated hydronephrotic sac; loculations due to connective tissue septums; complete destruction of the renal parenchyma.

tion of the ureter and pelvis about the constriction. The kidney was slightly atrophied; it weighed 33 gm. The opposite kidney weighed 37 gm.

Experiments 21 and 22 show the necessity of using permanent ligating material when complete obstruction of the ureter is desired, since absorbable ligatures may produce only partial constriction, and atrophy of the kidney may ensue.

The experiments on this group of dogs conclusively demonstrate these points:

1. Sudden complete occlusion of the ureter produces a hydronephrosis in every instance, the degree depending on the duration of the obstruction.

2. The hydronephrotic cavity is developed by dilatation of the pelvis and atrophy of the renal parenchyma and of the walls of the kidney.

3. The atrophic changes are quite uniform in distribution but vary in different animals.

4. The kidney is capable of secreting after thirty-six days of complete ureteral obstruction.

5. The renal blood vessels are the last structures to be affected by the increased intrarenal pressure.

6. In every instance the capsular veins are dilated, the enlargement depending on the amount of hydronephrosis.

Group 2. Double Ligation and Section of One Ureter and the Collateral Venous Circulation (Thirty-One Experiments).—The consistency with which dilatation of the capsular veins accompanied hydronephrosis led to the experiments in Group 2.

The collateral veins are ordinarily too small to be noticed in the normal kidney. The dilatation of these veins during the development of hydronephrosis and the observation that their enlargement seems to be dependent on the amount of renal distention brought up the question of whether they were one of the causative factors in the production of the hydronephrosis or whether they were the result of the hydronephrosis. In order to determine the point, the capsular blood supply was blocked by ligation at the same time as the ureter. Tuffier and Lejars,[6] working on the collateral circulation, ligated the renal vein and found that the renal venous blood is returned to the general circulation by four routes; (1) the inferior diaphragmatic and suprarenal vessels, (2) the ureteric and spermatic vessels, (3) the subcutaneous plexus of the lumbar region, and (4) the plexus which surrounds the last intercostal nerve, the ileo-inguinal nerve and the ileohypogastric nerve.

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6. Tuffier and Lejars: Les veines de la capsule adipeuse du rein, Arch. de Physiol. norm. et path. **3**:41-57, 1891.

The technic of the operative procedure in Group 2 differed from that in Group 1 in that after the collateral circulation was carefully dissected out and the ureter freed, both were doubly ligated and sectioned so that the only blood entering or leaving the kidney was that which passed through the renal artery and vein. A definite hydronephrosis was produced in each instance, and its progress was essentially the same as those in Group 1 except that it developed more slowly and to a less degree than when the collateral circulation was left intact. Frequently

TABLE 2.—SERIES I: THE EFFECT ON THE KIDNEY AND URETER OF COMPLETE SUDDEN OCCLUSION OF THE URETER OR OF THE COLLATERAL VENOUS CIRCULATION

Group 2: Double Ligation and Section of One Ureter and the Collateral Circulation (Thirty-One Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ureter Ligated	Necropsy	Pyonephrosis	Hydronephrosis	Adhesions Around Kidney Operated On	Condition of Kidney not Operated On
1 (581)	C697	8/12/18	453	Left	530	..	Large	0	Normal
2 (636)	C730	8/26/18	422	Left	498	..	Moderate	0	Normal
3 (35)	B724	1/13/17	337	Left	658	..	Moderate	+	Hypertrophic
4 (34)	B723	1/13/17	297	Left	592	+	Large	+	Hypertrophic
5 (430)	C 6	5/28/17	217	Right	677	..	Moderate	+	Hypertrophic
6 (582)	C106	8/28/17	200	Left	105	+	Large	+	Hypertrophic
7 (40)	B729	1/20/17	159	Left	396	..	Large	Omentum	Normal
8 (421)	B997	5/25/17	150	Right	555	..	Large	0	Normal
9 (32)	B721	1/13/17	149	Left	363	..	Large	0	Normal
10 (637)	C731	8/26/18	115	Left	702	..	Large	Omentum	Hypertrophic
11 (435)	C 11	6/ 1/17	98	Right	402	+	Large	+	Normal
12 (422)	B996	5/25/17	59	Right	436	..	Moderate	0	Normal
13 (410)	B990	5/14/17	35	Right	380	..	Moderate	0	Normal
14 (580)	C104	8/20/17	34	Left	527	+	Moderate	+	Normal
15 (503)	C 92	8/10/17	32	Left	518	+ ruptured	Large	Omentum	Normal
16 (522)	C 70	6/27/17	27	Left	475	..	Moderate	Omentum	Normal
17 (33)	B722	1/ 3/17	24	Left	52	..	Large	0	Hypertrophic
18 (483)	C608	7/15/18	23	Left	428	..	Moderate	0	Normal
19 (30)	B709	1/ 9/17	23	Left	37	..	Large	+	Normal
20 (525)	C 72	7/27/17	22	Left	490	..	Large	0	Normal
21 (420)	B996	5/25/17	19	Right	368	..	Moderate	+	Normal
22 (41)	B730	1/20/17	17	Left	51	..	Moderate	0	Normal
23 (502)	C627	7/22/18	17	Left	434	..	Small	0	Normal
24 (19)	B708	1/ 9/17	16	Left	40	..	Small	+	Normal
25 (411)	B991	5/14/17	10	Right	336	..	Small	+	Normal
26 (545)	C666	8/ 5/18	10	Right	457	..	Small	0	Normal
27 (545)	C 84	8/ 3/17	9	Left	468	..	Small	0	Normal
28 (522)	C646	7/29/17	8	Left	419	..	Small	0	Normal
29 (580)	C696	8/12/18	5	Right	463	..	Small	Omentum	Normal
30 (722)	C161	10/26/17	5	Right	582	..	Small	0	Normal
31 (503)	C628	7/22/18	4	Left	393	..	Small	0	Normal

the kidney and its hydronephrotic sac were found to be smaller than the opposite normal kidney, in spite of the distinct hydronephrotic cavity produced by the progressive atrophy of the renal parenchyma (Table 2 and Figs. 9 to 22).

In Experiments 1 and 4, of 453 and 297 days' obstruction, respectively, the hydronephrotic sacs were the largest in the group, but not so large as those in Group 1 in which the ureter alone was ligated. In

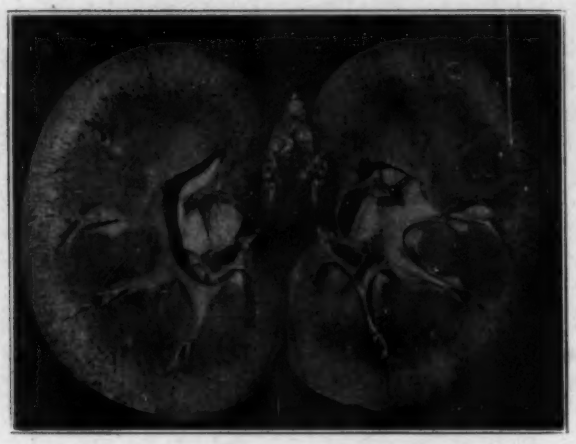

Fig. 9 (Series I, Group 2, Experiment 29 [C 696]).—Ligation of the ureter and collateral blood supply, five days' duration; small hydronephrosis; flattening of the renal papillae and thinning of the medulla.

Fig. 10 (Series I, Group 2, Experiment 25 [B 991]).—Ligation of the ureter and the collateral blood supply, ten days' duration; small hydronephrosis; destruction of renal parenchyma in lateral portions, median sagittal portion still preserved; opposite kidney normal.

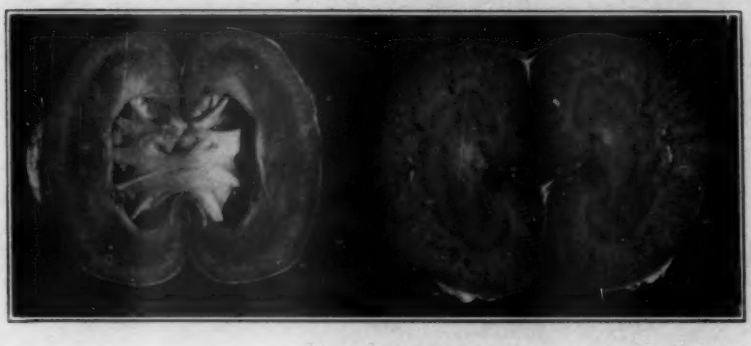

Fig. 11 (Series I, Group 2, Experiment 23 [C 627]).—Ligation of the ureter and the collateral blood supply, seventeen days' duration; small hydronephrosis; opposite kidney normal.

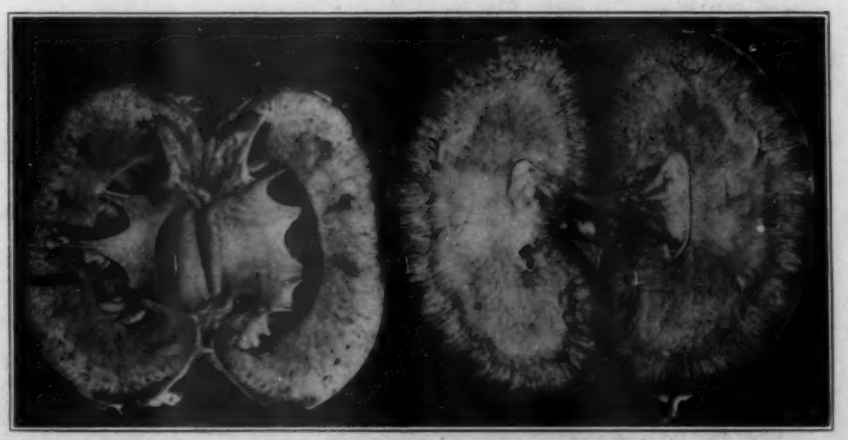

Fig. 12 (Series I, Group 2, Experiment 18 [B 608]).—Ligation of the ureter and the collateral blood supply, twenty-three days' duration; large hydronephrotic cavity with atrophy of the kidney; opposite kidney normal.

Fig. 13 (Series I, Group 2, Experiment 17 [B 722]).—Ligation of the ureter and the collateral blood supply, twenty-four days' duration; large hydronephrotic sac; atrophy of the kidney, particularly in the lateral portions; opposite kidney normal.

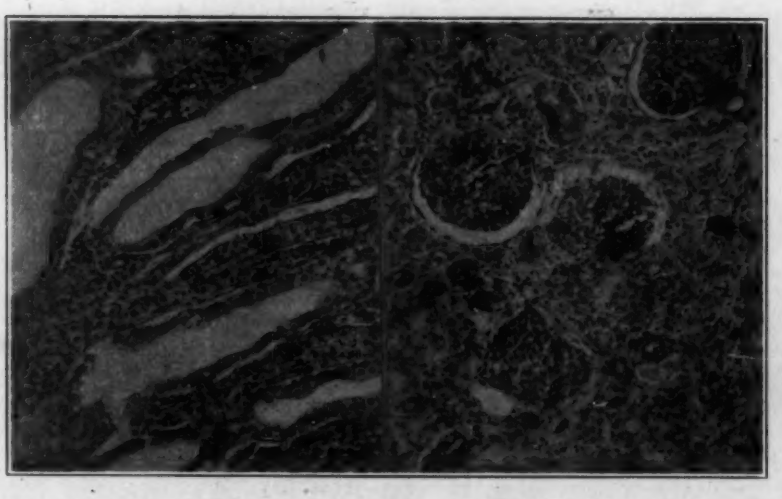

Fig. 14 (Series I, Group 2, Experiment 17 [B 722]).—Degeneration of the convoluted tubules; dilatation of the collecting tubules and glomeruli of kidney shown in Figure 13.

Fig. 15 (Series I, Group 2, Experiment 15 [C 92]).—Ligation of the ureter and the collateral blood supply, thirty-two days' duration; large pyonephrosis which ruptured, causing peritonitis and death.

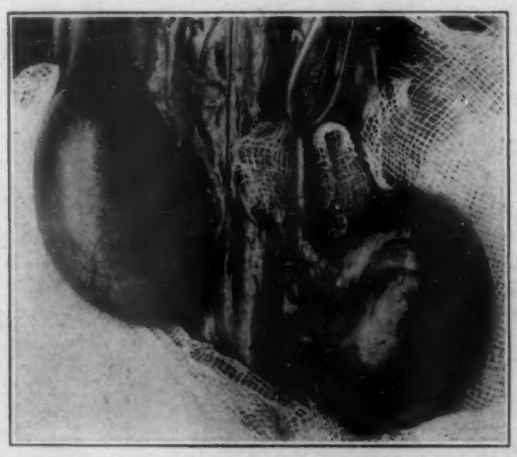

Fig. 16 (Series I, Group 2, Experiment 13 [B 990]).—Ligation of the ureter and the collateral blood supply, thirty-five days' duration; no dilatation of capsular vessels; large hydronephrotic cavity with atrophy of the kidney; with hydronephrotic sac smaller than opposite normal kidney.

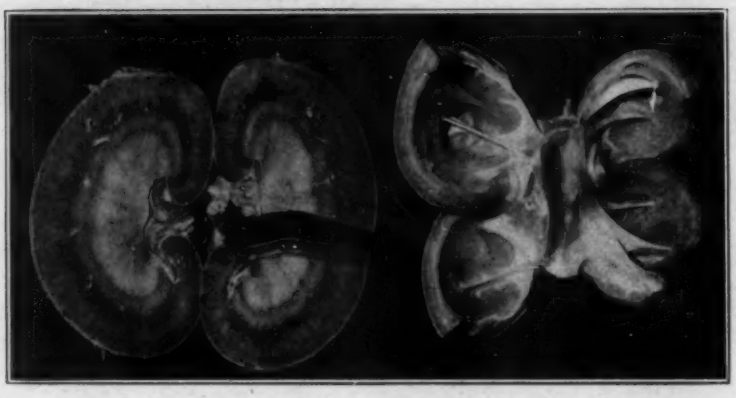

Fig. 17 (Series I, Group 2, Experiment 13 [B 990]).—Ligation of the ureter and the collateral blood supply, thirty-five days' duration; no dilatation of capsular vessels; large hydronephrotic cavity with atrophy of the kidney; kidney with hydronephrotic sac smaller than opposite normal kidney.

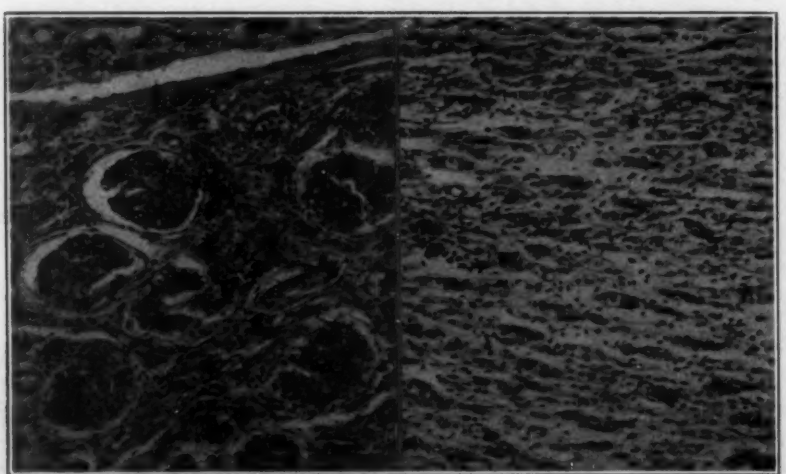

Fig. 18 (Series I, Group 2, Experiment 13 [B 990]).—Marked degeneration of tubules of cortex and medulla of kidney shown in Figures 16 and 17; glomeruli fairly well preserved in cortical portion proximal to the capsule.

Fig. 19 (Series I, Group 2, Experiment 9 [B 721]).—Ligation of the ureter and the collateral blood supply, 149 days' duration; no dilatation of the capsular veins; large hydronephrotic kidney with dilated tortuous ureter; hydronephrotic kidney lower than opposite normal kidney.

Fig. 20 (Series I, Group 2, Experiment 8 [B 997]).—Ligation of the ureter and the collateral blood supply, 150 days' duration; large hydronephrotic sac; complete destruction of renal parenchyma with persistence of connective tissue bands between the lobules; opposite kidney normal.

Fig. 21 (Series I, Group 2, Experiment 2 [C 730]).—Ligation of the ureter and the collateral blood supply, 422 days' duration; large hydronephrotic sac with almost complete destruction of the renal parenchyma except in the median saggital portion; opposite kidney normal.

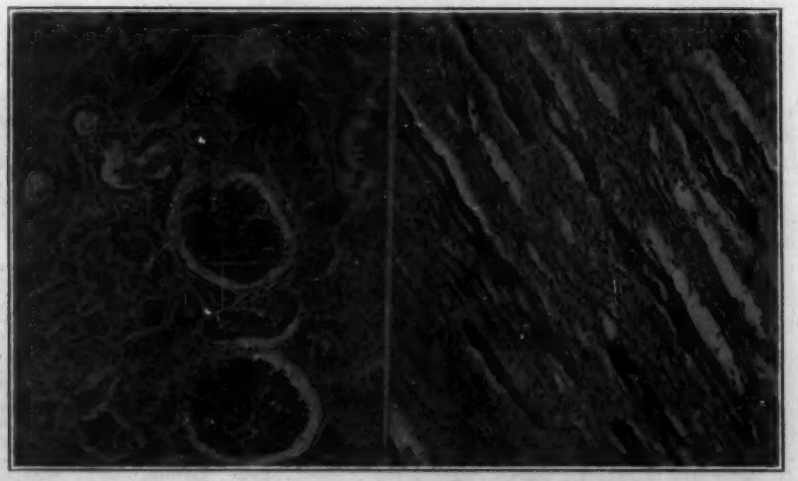

Fig. 22 (Series I, Group 2, Experiment 2 [C 730]).—Ligation of the ureter and the collateral blood supply, 422 days' duration; marked degeneration of the renal parenchyma of kidney shown in Figure 21; glomeruli well preserved.

Experiment 4, of 297 days' obstruction, the animal developed the largest hydronephrotic sac of the series. The kidney weighed 540 gm., and the sac contained 250 c.c. of purulent fluid. There were many adhesions about the kidney. In Experiment 1, of 453 days' ureteral obstruction, the kidney weighed 382 gm., and the sac contained 190 c.c. of clear fluid. The capsular vessels were not dilated.

In Experiments 2 and 3, of 422 and 337 days' duration, respectively, a moderate degree of hydronephrosis developed, the sacs containing 40 c.c. and 30 c.c. of fluid, respectively. No dilatation of the capsular vessels could be detected. In Experiment 2, the hydronephrotic kidney was smaller than the opposite normal kidney (Figs 21 and 22). The parenchyma was completely destroyed.

In Experiment 15 the animal appeared to be in good health the night of the thirty-second day but was found dead the next morning. At necropsy the cause of death was found to be the rupture of a large pyonephrotic sac which had produced a peritonitis. Many adhesions were found about the sac.

The animals in Experiments 4, 6, 11, 14, and 15 also developed pyonephrosis in the kidney operated on, which makes its incidence much higher in Group 2 than in Group 1, in which the collateral circulation was not interfered with.

In many of the animals there were adhesions of the omentum and of the structures adjacent to the kidney operated on, but not sufficient to have any bearing on the blood supply of the kidney.

From these experiments these conclusions may be drawn:

1. Hydronephrosis develops in the kidney of a dog following the ligation of one ureter and of the collateral blood supply.

2. The hydronephrotic sac is smaller and develops more slowly if the collateral circulation is intact.

3. Pyonephrosis is more common if the collateral circulation has been ligated.

4. Progressive atrophic changes occur in the kidney in the same sequence as when the ureter alone is ligated.

5. Ligation of the ureter does not affect the general health of the dog, since ten animals lived more than 100 days and two more than 400 days before being killed.

In summarizing the observations made in Groups 1 and 2 of Series I, it is important to note that after the outflow of urine is obstructed by ligating the ureter the normal secretion of urine continues until the ureter and pelvis of the kidney are completely filled; after that, urinary secretion takes place under the abnormal condition of back-pressure

from the damming up of urine in the pelvis of the kidney, which immediately dilates because its walls are elastic and not capable of resisting this increased intrapelvic pressure. The secreting power of the kidney is greatest at the time of ligation of the ureter, gradually diminishing in direct proportion to the duration of the obstruction, as the increased intrapelvic pressure causes a compression of the renal parenchyma by flattening of the pyramids and thinning of the medulla and cortex and a damming back of urine in the tubules. This exerts pressure directly on the cells lining the tubules and results in decreased nutrition and atrophy of the renal parenchyma. The increased intrapelvic and intrarenal pressures cause a compression of the small venous capillaries where only low pressure obtains, thus partially obstructing the venous return. This produces a congestion and edema of the kidney, but does not completely obstruct the venous return, and blood continues to pass from the kidney through the renal vein although the amount is greatly diminished, and the glomerulus is the last renal structure to be destroyed. The partial obstruction of the venous return affects the renal parenchyma and secretory power of the kidney in two ways. It decreases the amount of blood passing through the kidney and consequently the amount of secretion possible. Likewise the amount of nutrition carried to the cells of the parenchyma must be diminished. Partial obstruction of the venous return is relieved in two ways, first, by dilatation of the capsular veins, and second, by absorption from the medullary portion of the kidney, which is in inverse proportion to the destruction of the renal parenchyma. Dilatation of the capsular veins is caused by increased intrarenal pressure and is secondary to the production of hydronephrosis, since a hydronephrotic sac develops when the collateral circulation is ligated. The partial compensation of the venous return by the dilatation of the capsular vessels permits a greater secretory activity of the kidney because of the increased blood supply and nutrition and results in a larger and more rapidly developing hydronephrosis, which in turn causes more speedy destruction of the parenchyma than is found when the collaterals are ligated. The production of hydronephrosis is dependent on the amount of resistance afforded by the pelvis to the increased intrapelvic pressure incident to the secretory activity, which is variable, but greatest at the time of obstruction, and gradually diminishes so that in four weeks no secretion is demonstrable. It is possible that this may be the explanation of the difference in the results obtained in experimental investigations in animals and the clinical observations noted in man; that is, in man the collateral venous circulation is practically negligible, and the pelvis and capsule of the kidney are more resistant. It seems that if it were possible to enclose the pelvis of the kidney and the ureter in a plaster-of-Paris cast and completely obstruct

the outflow of urine, the increased intrapelvic pressure would become so great that it would stop all secretory activity and result in atrophy of the kidney.

SERIES II. THE EFFECT OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

The study of the results of ligation of the various vascular radicals of the kidney was undertaken with the view of determining the ultimate effect on the renal parenchyma and whether or not a collateral venous circulation would be established. It was shown by Bowman,[7] in 1842, that the arterial radicals of the kidney were end arteries, but Hyrtl,[8] in 1882, was first to point out that there was no anastomosis between the branches of the renal arteries. These facts are often lost sight of by surgeons in various surgical procedures upon the kidney, as mentioned by Brödel,[9] in 1901.

Series II comprises four groups. The experiments in Groups 1 and 2 pertain to the arterial blood supply, and those in Groups 3 and 4, to the venous supply. The operative procedures were essentially the same in the four groups except that different vessels were ligated.

Group 1. Ligation of the Renal Artery (Five Experiments).—In this study it was my purpose to determine: (1) the results produced on the kidney, (2) whether or not a collateral blood supply would be established, and (3), whether or not the omentum when wrapped about a decapsulated kidney would furnish sufficient blood to continue the function of the kidney.

After the kidney was exposed, the renal artery was carefully dissected from the perirenal fat and doubly ligated and sectioned. As shown in Table 3, the renal artery alone was ligated in three dogs; the artery was ligated and the kidney decapsulated and wrapped in omentum in two.

Sudden complete occlusion of the renal artery by ligation resulted in a gradual symmetric atrophy of the entire kidney. In Experiments 1, 4, and 5, collateral arterial anastomosis was not formed. In Experiments 2 and 3, of sixteen and ten days' duration, the kidney was wrapped in omentum, but this had no effect on the degree of atrophy of the kidney (Figs. 23, 24 and 25).

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7. Bowman, W.: On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation Through That Gland, London, Taylor, 1842.

8. Hyrtl, J.: Lehrbuch der Anatomie des Menschen, mit Rüchsicht auf physiologische Begründung und praktische Anwendung, Vienna, 1882, **1**:834, quoted by Brödel.

9. Brödel, M.: The Intrinsic Blood Vessels of the Kidney and Their Significance in Nephrectomy, Bull. Johns Hopkins Hosp. **12**:10-13, 1901.

From these five experiments it is evident that (1) the renal artery is the only source of blood supply to the kidney, furnishing both nutritional and functional blood, and is a strict end artery; (2) a collateral arterial anastomosis is not formed after ligation of the renal artery, and (3) wrapping the kidney in omentum after decapsulation and ligation of the renal artery does not produce arterial anastomosis in order to supply the renal parenchyma and therefore has no effect on the development of atrophy.

Group 2. Ligation of One or More Branches of the Renal Artery (Sixteen Experiments).—In man it is frequently necessary to ligate an aberrant vessel passing to the lower pole of the kidney, causing an intermittent obstruction to the outflow of urine and producing a hydronephrosis.

In sixteen animals after the kidney was exposed, the branches of the renal artery were carefully dissected free from perirenal fat and one or more doubly ligated and sectioned (three to 526 days' duration) with

TABLE 3.—SERIES II: THE EFFECT OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

Group 1: Ligation of Renal Artery (Five Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Renal Artery Ligated	Decapsulation of Kidney and Wrapping in Omentum	Necropsy	Kidney Tissue Pale and Degenerating	Collateral Arterial Circulation	Atrophy of Kidney Oper. On	Wt. of Kidney Oper. on. Gm.	Adhesions Around Kidney Operated On	Wt. of Kidney Not Oper. On Gm.
1 (190)	B828	3/ 5/17	31	Left	...	214	+	0	+	10	.....	40
2 (99)	B769	2/10/17	16	Left	+	90	+	0	+	18	Omentum	27
3 (53)	B742	1/27/17	10	Left	+	53	+	0	+	14	Omentum	26
4 (242)	B869	3/16/17	8	Left	...	173	+	0	+	30	.....	45
5 (490)	C 47	7/ 9/17	4	Right	...	419	+	0	+	38	.....	42

the view of determining as accurately as possible what may be expected in man if for any reason the same procedure is necessary. In the dog there are usually four branches of the renal artery, two to the anterior surface and two to the posterior surface. The anterior vessels are the larger; they supply the anterior two thirds of the kidney; the smaller posterior branches supply approximately the posterior third. They usually divide just inside the hilum into two smaller branches, one to each pole. For convenience of description these vessels have been termed anterior superior and inferior, and posterior superior and inferior, the areas of the kidney to which they pass being designated quadrants according to the vessel. This division on the basis of the distribution of the arterial branches is not accurate since the posterior branches supply less kidney tissue than the anterior vessels, and there is also a variation in the size of the superior and inferior branches, the size of the vessel being in accordance with the area supplied.

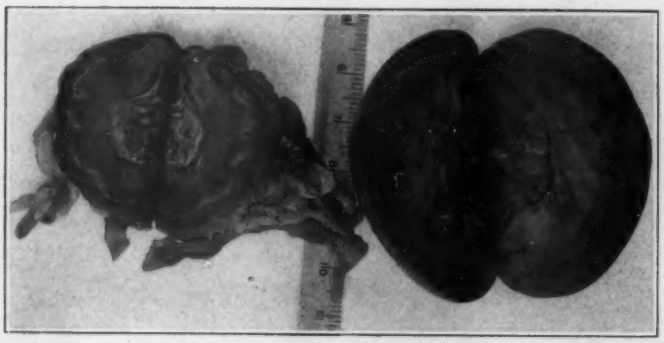

Fig. 23 (Series II, Group 1, Experiment 2 [B 769]).—Ligation of the left renal artery, kidney wrapped in omentum, sixteen days' duration; atrophy of the entire kidney which weighed 10 gm. Wrapping kidney in omentum did not affect the result.

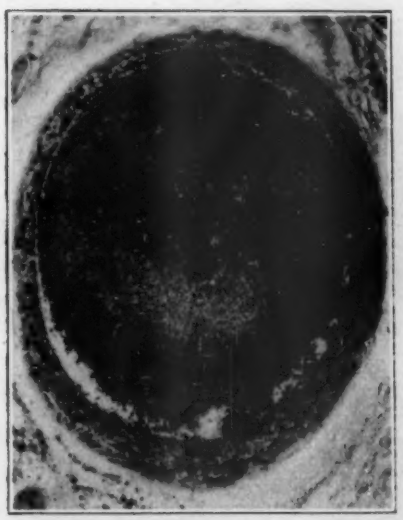

Fig. 24 (Series II, Group 1, Experiment 2 [B769]).—Section of kidney shown in Figure 23; thrombosis of kidney vessels.

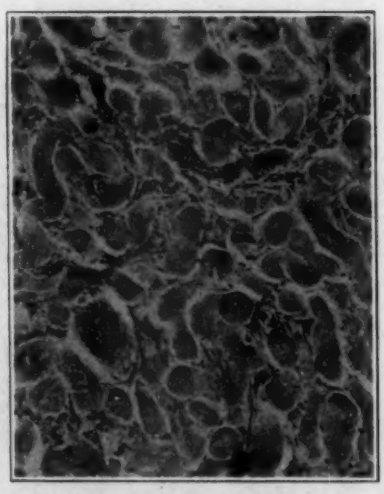

Fig. 25 (Series II, Group 1, Experiment 2 [B769]).—Section of kidney shown in Figure 23; ambyloid degeneration of the renal parenchyma of the cortex and medulla.

Immediately following ligation of a branch of the renal artery there was marked congestion of the portion of kidney supplied by that vessel, and a bluish discoloration of the cortex with a sharp line of demarcation was produced. A linen thread was sutured accurately around the margin of this area so that it would be possible to determine whether or not the circulation in any part of the area was later restored and what the ultimate fate of this portion of the renal parenchyma was (Table 4, and Figs. 26 to 32).

TABLE 4.—Series II: The Effect of Occlusion of the Various Vascular Radicals of the Kidney

Group 2: Ligation of One or More Branches of the Renal Artery (Sixteen Experiments)

Experiment	Animal	Date of Operation	Renal Artery Ligated	Branches of Renal Artery Ligated				Duration of Experiment, Days	Decapsulation of Kidney and Wrapping in Omentum	Necropsy	Atrophy of Kidney			
				Anterior Superior	Anterior Inferior	Posterior Superior	Posterior Inferior				Anterior Superior Quadrant	Anterior Inferior Quadrant	Posterior Superior Quadrant	Posterior Inferior Quadrant
1 (273)	C444	4/29/18	Right	+	..	..	+	526	+	464	+	..	..	+
2 (442)	C509	7/ 1/18	Right	..	..	..	+	464	..	465	..	..	..	+
3 (398)	C529	6/17/18	Right	..	..	+	+	...	..	...	..	..	+	+
			Left	+	..	+	..	348	+	261	+	..	+	..
4 (265)	C438	4/22/18	Right	..	..	+	+	325	+	93	..	..	+	+
5 (331)	C477	5/20/18	Right	..	+	+	+	43	..	326	..	+	+	+
6 (364)	C505	6/ 3/18	Right	+	..	+	..	...	..	...	..	..	+	..
			Left	..	+	+	+	38	+	347	..	+	+	+
7 (274)	C445	4/29/18	Right	+	+	..	+	...	..	...	+	+	+	+
			Left	..	..	+	..	23	..	261	..	..	+	..
8 (235)	C412	4/ 4/18	Right	..	..	+	+	15	+	220	..	..	+	+
9 (291)	C456	5/ 6/18	Right	+	+	..	..	...	..	...	+	+	..	..
			Left	+	+	..	..	14	..	258	+	+	..	..
10 (236)	C413	4/ 8/18	Right	..	..	..	+	11	..	218	..	..	..	+
11 (257)	C430	4/15/18	Right	+	+	..	..	10	..	230	+	+	..	..
12 (329)	C476	5/20/18	Left	+	+	..	..	7	..	271	+	+	..	..
13 (256)	C429	4/15/18	Right	..	..	+	+	4	..	219	..	..	+	+
14 (225)	C402	4/ 4/18	Right	+	+	..	..	4	..	180	+	+	..	..
15 (224)	C401	4/ 4/18	Right	..	..	+	+	4	..	179	..	..	+	+
16 (363)	C504	6/ 3/18	Right	..	..	+	+	...	..	...	..	..	+	+
			Left	..	..	+	..	3	..	283	..	..	+	..

These experiments show quite conclusively that (1) ligation of any branch of the renal artery causes atrophy of the area of renal parenchyma supplied by it; (2) each branch entering the kidney carries functional and nutritional blood to its respective area, and (3) there is no anastomosis between any of the branches of the renal artery.

Group 3. Ligation of the Renal Vein (Eight Experiments).—This phase of the problem was studied in order to determine (1) the results produced on the kidney; (2) whether or not a collateral venous circulation would be established and if so of what veins it would be comprised, and (3) whether or not this collateral venous circulation would be capable of assuming the function of the renal vein and of maintaining a functionating kidney.

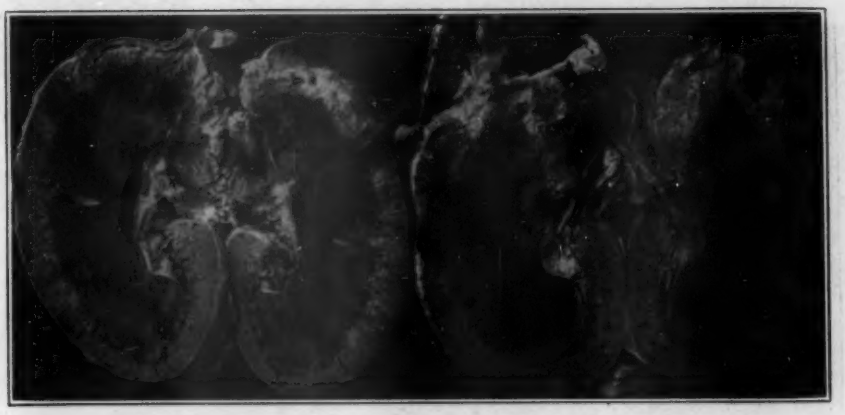

Fig. 26 (Series II, Group 2, Experiment 16 [C 504]).—Ligation of the posterior superior branch of left renal artery and of the posterior superior and inferior branches of the right renal artery, three days' duration; degeneration of the posterior poles and areas supplied by these branches.

Fig. 27 (Series II, Group 2, Experiment 11 [C 430]).—Ligation of the anterior, superior and inferior branches of the right renal artery, ten days' duration; atrophy of the anterior pole of the right kidney; left kidney normal.

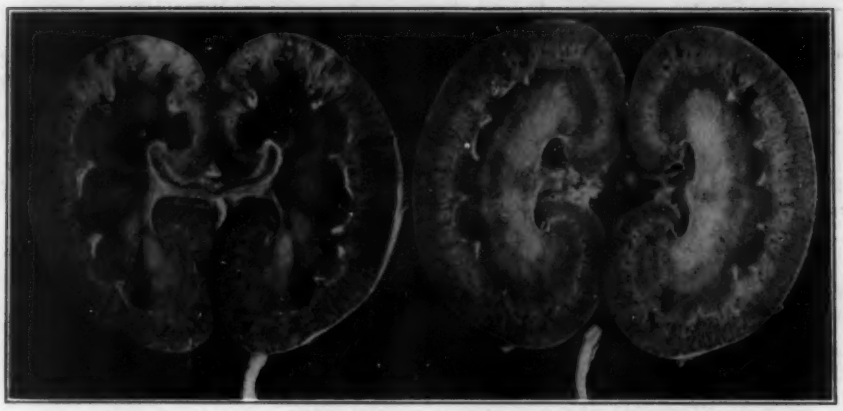

Fig. 28 (Series II, Group 2, Experiment 11 [C 430]).—Ligation of the anterior, superior and inferior branches of the right renal artery, ten days' duration. Atrophy of the anterior pole of the right kidney. Left kidney normal.

Fig. 29 (Series II, Group 2, Experiment 10 [C 413]).—Ligation of the posterior inferior branch of the right renal artery, eleven days' duration; atrophy of the renal tissue supplied by this branch; left kidney normal.

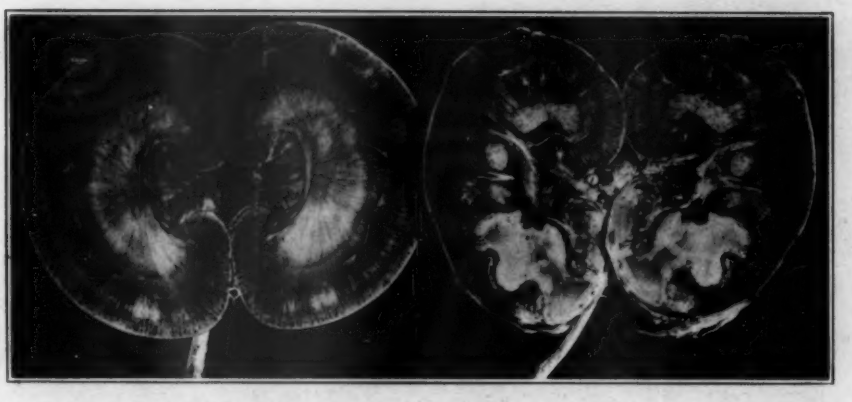

Fig. 30 (Series II, Group 2, Experiment 8 [C 412]).—Ligation of the posterior superior and inferior branches of the right renal artery; right kidney decapsulated and wrapped in omentum, fifteen days' duration; atrophy of the lower pole of the right kidney supplied by the posterior branch; results not affected by decapsulation and wrapping in omentum; new capsule formed in right kidney.

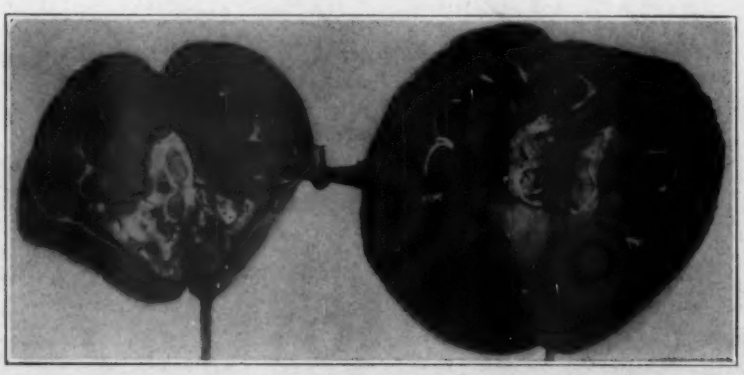

Fig. 31 (Series II, Group 2, Experiment 6 [C 505]).—Ligation of the anterior superior and posterior superior branches of the right renal artery and of the anterior inferior and posterior inferior branches of the left renal artery; both kidneys decapsulated and wrapped in omentum, thirty-eight days' duration; atrophy of area supplied by these vessels; no effects from wrapping kidney in omentum; new capsule formed in both kidneys.

Lindemann,[10] in 1898, stated that after the renal vein is obstructed, a collateral circulation is developed sufficient to maintain the function of the kidney. Téstut,[11] in 1917, stated that the collateral circulation is capable of maintaining the renal function in part. Tuffier and Lejars [6] stated that obliteration of the renal vein results in the formation of a collateral circulation whereby venous blood from the kidney is carried back to the general circulation through this plexus by four routes: (1) suprarenal and inferior diaphragmatic, (2) ureteric and spermatic or

Fig. 32 (Series II, Group 2, Experiment 4 [C436]).—Ligation of the posterior superior and inferior branches of the right renal artery; right kidney decapsulated and wrapped in omentum, 325 days' duration; atrophy of the posterior half of the right kidney; no effects from decapsulation and wrapping kidney in omentum.

ovarian, (3) subcutaneous plexuses of the lumbar veins, and (4) a plexus which surrounds the last intercostal, ileo-inguinal, and ileohypogastric nerves.

After the kidney was exposed the renal vein was carefully dissected from the perirenal fat at the hilum and doubly ligated and sectioned (Table 5).

Immediately after the renal vein was ligated there was a marked enlargement and bluish discoloration of the kidney from venous congestion. The organ became very tense from the engorgement of blood. This was followed almost immediately by dilatation of the capsular vessels, especially the suprarenal, the ovarian or spermatic, and branches

10. Lindemann, W.: Ueber Veränderungen der Nieren infolge von Ureterunterbindung, Ztschr. f. klin. Med. **34**:299-321, 1898.

11. Téstut, J. L.: Traité d'anatomie humaine, Ed. 6, Paris, O. Doin, 1911-1912.

to the lumbar veins. In a few instances, a vein was found passing directly from the capsule of the kidney to the renal vein. In most instances two or more of these dilated capsular vessels were found.

In Experiments 5, 6, 7, and 8, of six, four, four, and two days' duration, respectively, there was marked congestion and enlargement of the kidney with beginning degenerative changes (Figs. 33, 34 and 35).

In Experiment 6 the dog died on the fourth day. At necropsy it was found that death was caused by hemorrhage from the kidney operated on, which had ruptured in several places (Figs. 33 and 34), allowing the blood to escape and infiltrate the surrounding tissues. This kidney weighed 200 gm. and showed enormous congestion throughout the parenchyma.

TABLE 5.—SERIES II: THE EFFECT OF OCCLUSION OF THE VASCULAR RADICALS OF THE KIDNEY

Group 3: Ligation of the Renal Vein (Eight Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ligation of Renal Vein	Necropsy	Dilatation			Lumbar Veins	Congestion of Kidney Operated On	Atrophy of Kidney Operated On	Weight of Kidney Operated On, Gm.	Weight of Kidney Not Operated On, Gm.
						Capsular Veins	Suprarenal Veins	Ovarian or Spermatic Veins					
1 (156)	B804	2/26/17	345	Left	49	+	+	+	+	.	+	5	30
2 (291)	B902	3/26/17	132	Right	453	+	+	+	..	..	+	4	20
3 (50)	B739	1/27/17	12	Left	55	+	..	+	+	+	+	24	30
4 (418)	C548	6/24/18	10	Left	336	+	+	+	..	+	+	25	37
5 (126)	B795	2/19/17	6	Left	87	+	+	+	+	+	..	34	30
6*(246)	B871	3/17/17	4	Left	164	..	..	..	..	..	..	200	57
7 (240)	B868	3/16/17	4	Left	152	+	+	+	..	+	..	30	20
8 (304)	B913	3/28/17	2	Left	190	+	+	+	..	+	..	32	25

* Kidney ruptured in several places; hemorrhage cause of death.

In Experiments 3 and 4, of twelve and ten days' duration, respectively, there was beginning atrophy of the entire kidney. In both there was pronounced dilatation of the capsular veins.

In Experiments 1 and 2, of 132 and 345 days' duration, respectively, there was a marked atrophy of the entire kidney. In Experiment 1, only a small nodule of kidney tissue was left. In Experiment 2, the remaining kidney tissue was symmetrically atrophied and weighed 4 gm. at the end of 345 days (Fig. 36).

This group of experiments shows that (1) there is symmetrical atrophy of the kidney after complete sudden occlusion of the renal veins; (2) a partial venous collateral circulation to the kidney is established comprising chiefly the ovarian or spermatic veins, the suprarenal veins, and branches of the lumbar veins; (3) the collateral circulation of the kidney is not capable of assuming the function of the renal vein

Fig. 33 (Series II, Group 3, Experiment 6 [B 871]).—Ligation of the left renal vein, four days' duration; rupture of the left kidney from engorgement of blood, causing death from hemorrhage; right kidney normal.

Fig. 34 (Series II, Group 3, Experiment 6 [B 871]).—Ligation of the left renal vein, four days' duration; rupture of the left kidney from engorgement of blood, causing death from hemorrhage; right kidney normal.

Fig. 35 (Series II, Group 3, Experiment 5 [B 795]).—Ligation of the left renal vein, six days' duration; marked congestion of left kidney, weight 34 gm.; right kidney normal, weight 36 gm.

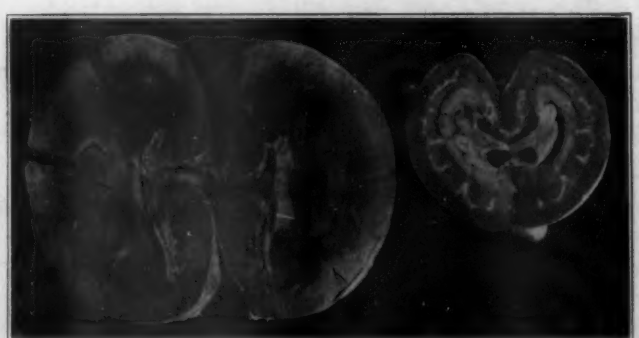

Fig. 36 (Series II, Group 3, Experiment 5 [B 795]).—Ligation of the right renal vein, 132 days' duration; atrophy of entire kidney, weight 4 gm.; left kidney normal, weight 20 gm.

and maintaining a functionating kidney, and (4) ligation of the renal vein in a dog may cause the kidney to rupture.

Group 4. Ligation of One of the Larger Branches of the Renal Vein (Two Experiments).—This work was undertaken with the view of determining whether or not the capsular vessels would be dilated after partial obstruction of the venous return from the kidney, and whether or not the venous radicals of the kidney would anastomose.

The surgical procedure was the same as that used in former groups except that after the kidney was exposed the larger of the two main branches of the renal vein was dissected free from the perirenal fat and doubly ligated and sectioned. Two experiments were performed (Table 6).

TABLE 6.—SERIES II: THE EFFECTS OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

Group 4: Ligation of One of the Larger Branches of the Renal Vein

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ligation of Renal Vein	Ligation of One Branch of Renal Vein	Necropsy	Congestion of Kidney Operated On	Atrophy of Kidney Operated On	Weight of Kidney Operated On, Gm.	Weight of Kidney Not Operated On, Gm.
1 (416)	C546	6/24/18	359	Right	Posterior anterior	283	0	0	32 right	34 left
2 (393)	C524	6/10/18	37	Left	Posterior	572	0	0	34	37

In Experiment 1, the dog was killed after 359 days. At necropsy it was found that the kidney was normal in size and that no change had taken place in the renal parenchyma but the capsular vessels were slightly dilated.

In Experiment 2, the animal died on the thirty-seventh day. At necropsy the kidney was found to be normal in size, and there was no change in the renal parenchyma, but a moderate dilatation of the capsular vessels (Fig. 37).

SERIES III. THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

The frequency with which the ureter is accidentally and unavoidably traumatized during the course of various surgical procedures is very hard to determine. It is known that the ureter is sometimes accidentally clamped with an artery forceps during operations in the vicinity.

Group 1. Clamping of the Ureter (Eleven Experiments).—A review of the literature did not reveal any record of other studies of the effect on the kidney and ureter of clamping the ureter.

The operative procedure was essentially the same as that used in Series II. The ureter was exposed and crushed with a Kocher artery forceps for from one to thirty minutes and then replaced behind the peritoneum.

The eleven experiments of from four to 251 days' duration do not complete the investigation, but Table 7 indicates the results obtained to date (Figs. 38, 39 and 40).

TABLE 7.—SERIES III: THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

Group 1: Clamping the Ureter (Eleven Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ureter Clamped	Minutes Ureter Clamped	Notch of Kocher Clamp	Necropsy	Condition of Clamped Ureter			Appearance of Kidney With Clamped Ureter	Hydronephrosis	Dilatation of Capsular Veins
								Area of Degeneration	Partial Constriction	Dilatation			
1 (349)	B953	4/16/17	251	Right	10	Third	619	..	+	+	Normal	Marked (weight 18 gm.)	0
2 (262)	B883	3/19/17	36	Right	30	Fourth	278	..	+	7 to 8 times	Normal (weight 34 gm.)	Slight	0
3 (348)	B952	4/16/17	23	Right	30	Third	318	..	Slight	Slight	Normal	.....	0
4 (191)	B829	3/ 5/17	20	Right	5	Second	194	..	+	0	Normal	.....	0
5 (192)	B830	3/ 5/17	10	Right	10	Second	144	+	+	0	Normal	.....	0
6 (260)	B881	3/19/17	7	Right 2 times	3	Second	181	+	+	0	Normal	.....	0
7 (225)	B799	3/13/17	6	Left 4 times	1	Second	148	Slight	..	0	Normal	.....	0
8 (664)	B746	9/ 9/18	5	Left	45	Second	523	+	+	+	Normal	.....	0
9 (333)	B937	4/ 7/17	5	Right	30	Third	253	+	+	2 times	Normal	.....	0
10 (318)	B923	4/ 2/17	4	Right	30	Fourth	215	..	+	4 times	Normal	Small	0
11 (379)	B974	4/30/17	4	Left	30	Third	417	+	..	Slight	Normal	.....	0

Experiment 1 demonstrates the end-results on the kidney. The right ureter was crushed with a Kocher clamp to the third notch for ten minutes. The animal was killed in 251 days. The ureter was almost completely constricted, but water could be forced through the constricted area with a piston syringe. Both the ureter and pelvis were moderately dilated above the point of constriction. The kidney was small with a large hydronephrotic cavity (Fig. 40), the parenchyma being almost entirely destroyed by pressure atrophy. The entire organ weighed 18 gm. The capsular veins were not dilated, but there was compensatory hypertrophy of the opposite kidney which weighed 50 gm. The condition was very similar to that found in Group 2 of Series I, in which the ureter and the collateral veins were doubly ligated and sectioned.

In Experiment 2, the right ureter was clamped with a Kocher forceps to the fourth notch for thirty minutes. The dog died in thirty-six days. At necropsy a partial constriction of the ureter was found at the

Fig. 37 (Series II, Group 4, Experiment 2 [C 524]).—Ligation of one branch of the right renal vein, thirty-seven days' duration; right kidney normal.

Fig. 38 (Series III, Group 1, Experiment 10 [B 923]).—Clamping of the right ureter, thirty minutes; necropsy after four days; slight constriction of the right ureter which was dilated to four times its normal size; slight hydronephrosis of the right kidney; left kidney normal.

Fig. 39 (Series III, Group 1, Experiment 2 [B 883]).—Clamping of the right ureter, thirty minutes; necropsy after thirty-six days; partial constriction of the right ureter which was dilated to seven or eight times its normal size; slight hydronephrosis of right kidney.

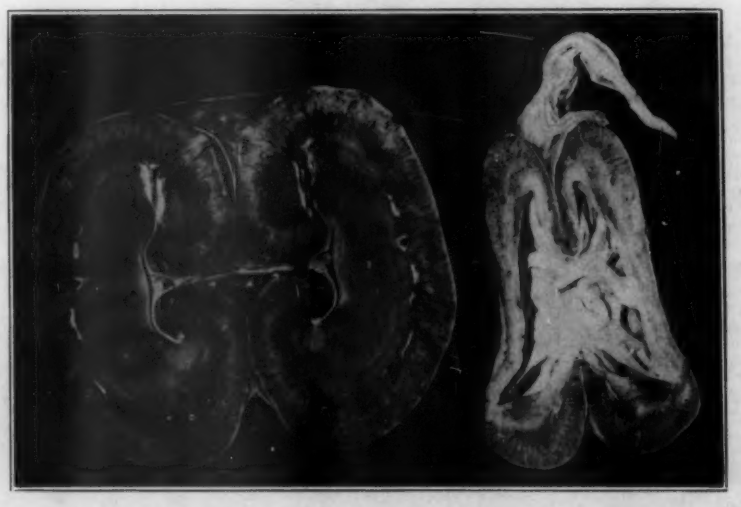

Fig. 40 (Series III, Group 1, Experiment 1 [B 953]).—Clamping of right ureter for ten minutes; necropsy after 251 days; partial constriction with dilatation of the right ureter; large hydronephrotic sac with atrophy of the right kidney; left kidney normal.

point of application of the clamp. The ureter was dilated from seven to eight times its normal size above the point of constriction, and three times the normal size below it. There was a moderate degree of dilatation of the pelvis, a small hydronephrotic cavity, and slight atrophy of the renal parenchyma. The kidney weighed 30 gm. The capsular veins were not dilated. The opposite kidney weighed 37 gm. (Fig. 39).

In Experiments 3 to 11, inclusive, of from four to twenty-three days' duration, there was a degenerating area at the point of application of the clamp which gradually formed into scar tissue, depending on the duration of the experiment. This scar tissue produced a stricture of the ureter with varying degrees of dilatation of the ureter above it (Fig. 38).

The study of this group of experiments shows that (1) injury to the ureter by crushing with artery forceps causes degenerative changes at the point of application, resulting in the formation of scar tissue which produces a partial constriction that may later progress to complete stricture; (2) there is dilatation of the ureter and pelvis in most instances which may progress to the point of hydronephrosis and degeneration of the kidney, with no dilatation of the capsular veins, and (3) no leakage of urine follows the application of a clamp to the ureter.

Group 2. Stripping of the Ureter.—In various surgical procedures on the kidney, ureter, and bladder, and in operations on other organs in their vicinity, it is often necessary to strip the ureter for a distance from the surrounding tissue. The practical significance of the extent to which this may be done is of the utmost importance to the surgeon because of its bearing on the end-results of various surgical procedures. Stewart and Barber,[12] in a series of nine experiments on dogs, produced ureteral paralysis by stripping the ureter of all nerve, vessel, and lymphatic connections from the pelvis of the kidney to the bladder. This ureteral paralysis was accompanied by urinary stasis and distention of the kidney in 66 per cent. of the cases.

Six experiments, ranging from fourteen to seventy-four days in duration, were performed in this group. The operative procedure is essentially the same in each instance. After the ureter was exposed, it was lifted from its bed and stripped with a piece of gauze for a distance of from 2 inches to its entire length and dropped back into the abdominal cavity with care to preserve as much of the blood supply as possible.

A study of the results obtained indicates that the ureter may be stripped of its surrounding tissues without permanent injury or dele-

12. Stewart, G. D., and Barber, W. H.: Hydronephrosis. An Experimental Study, Ann. Surg. **60**:723-728, 1914.

terious effect on the kidney, provided its blood supply is preserved, since pathologic change was not found in the kidney or ureter in a single instance (Table 8).

Group 3. Anastomosis of the Ureters (Twenty-Two Experiments).—Ureters are sometimes cut during the course of various surgical procedures in their vicinity, and not infrequently the ureter is severed by accident, fractures and so forth. In order to determine the best method of anastomosing these injured ureters, twenty-two experiments were performed. The operative procedure was the same as previously described, up to the point of exposing the ureter. The ureter was completely cut across in each instance.

TABLE 8.—SERIES III: THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

Group 2: Stripping the Ureter (Six Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Ureter Stripped With Gauze	Blood Supply Preserved	Distance of Stripping	Necropsy	No Change in Ureter	Condition of Kidney Operated On
1 (583)	C107	8/20/17	74	Left	+	Entire length	317	+	Normal
2 (536)	C 75	7/30/17	41	Right	+	10 cm.	372	+	Normal
3 (285)	B809	3/24/17	31	Right	+	7.5 cm.	277	+	Normal
4 (191)	B829	3/ 5/17	26	Left	+	5 cm.	194	+	Normal
5 (525)	C 72	7/27/17	22	Left	+	10 cm.	490	+	Normal
				Right	+	Entire length	...	+	Normal
6 (224)	B788	3/13/17	14	Left	+	Entire length	186	+	Normal

In five experiments (Method A) the cut ends of the ureter were anastomosed, end-to-end, with interrupted silk sutures. In thirteen experiments (Method B) the anastomosis was made by drawing the proximal end into the distal end for a distance of 0.625 cm., using three interrupted silk sutures, one at the lower end of the anastomosis and two at the upper end. In the remaining four experiments (Method C) the proximal end of the ureter was anastomosed into the side of the opposite ureter and sutured behind the peritoneum (Table 9).

Method A. End-to-End Anastomosis: Three of the five animals in this group (Experiments 1, 2, and 3) died the third day of peritonitis from urinary leakage. In Experiment 4, the animal died the nineteenth day from sepsis, resulting from an abscess which had formed at the site of the anastomosis and had burrowed into the pelvis, forming a large pocket of pus. In Experiment 5, the animal was killed the fifty-sixth day. At necropsy a slight constriction and dilatation and a slight hydronephrosis were found (Fig. 41).

Method B. Cuff Anastomosis: This group consists of thirteen experiments of from five to 223 days' duration. In Experiment 6, the animal died the fifth day of peritonitis from urinary leakage, the only case of urinary leakage in this group. In Experiments 7 and 10, the ureters were markedly narrowed at the point of anastomosis, causing a partial constriction and dilatation of the ureter above this point with atrophy of the kidney and a moderate degree of hydronephrosis. In the remaining ten experiments, the ureter was slightly constricted at the point of anastomosis, in most cases producing a slight dilatation of the ureter. Little or no effect was produced on the kidney in five cases, and a slight hydronephrosis in five cases (Figs. 40, 43 and 44).

TABLE 9.—SERIES III: THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

Group 3: Anastomosis of Ureters (Twenty-Two Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	End-to-End Anastomosis	Cuff Anastomosis	Uretero-Ureterostomy	Necropsy	Slight Constriction at Anastomosis	Marked Obstruction at Anastomosis	Dilatation of Ureter Above Anastomosis	Urinary Leakage	Condition of Kidney Operated On
A1 (313)	B920	3/31/17	3	Right	.....	.....	199	..	..	..	+	
A2 (443)	C 19	6/11/17	3	Right	.....	.....	371	..	..	..	+	
A3 (483)	C 43	7/ 6/17	3	Right	.....	.....	413	..	..	..	+	
A4 (314)	B921	3/31/17	19	Right	.....	.....	233	..	.	..	+	
A5 (334)	B938	4/ 9/17	56	Right	.....	.....	344	..	..	Slight	0	Slightly hydronephrotic
B6 (452)	C 28	6/22/17	5	.....	Right	.....	397	..	..	..	+	
B7 (617)	C127	8/31/17	14	.....	Right	.....	522	+	+	..	0	Atrophic
B8 (600)	C119	8/27/17	18	.....	Right	.....	560	+	.	Slight	0	Normal
B9 (469)	C 36	7/ 2/17	36	.....	Right	.....	460	+	..	0	0	Normal
B10 (489)	C 46	7/ 9/17	43	.....	Right	.....	493	+	+	+	0	Atrophic
B11 (454)	C 30	5/25/17	48	.....	Right	.....	469	0	..	Slight	0	Normal
B12 (589)	C112	8/24/17	49	.....	Right	.....	538	+	..	Slight	0	Slightly hydronephrotic
B13 (630)	C135	9/10/17	60	.....	Right	.....	597	0	..	Slight	0	Normal
B14 (336)	B940	4/ 9/17	67	.....	Right	.....	373	+	..	Slight	0	Hydronephrotic
B15 (625)	C131	9/ 7/17	81	.....	Right	.....	623	0	..	Slight	0	Normal
B16 (599)	C118	8/27/17	95	.....	Right	.....	633	+	..	Slight	0	Hydronephrotic
B17 (453)	C 29	6/22/17	187	.....	Right	.....	611	0	..	Slight	0	Normal
B18 (455)	C 31	6/25/17	223	.....	Right	.....	8	+	..	+	0	Hydronephrotic
C19 (470)	C 37	7/ 2/17	2	.....	.....	Right into left	402	.	..	..	+	
C20 (498)	C 55	7/13/17	3	.....	.....	Right into left	420	..	..	..	+	
C21 (499)	C 56	7/13/17	4	.....	.....	Right into left	423	..	..	..	+	Left, hydronephrotic
C22 (491)	C 48	7/ 9/17	25	.....	.....	Right into left	44.	..	+	..	0	Left, atrophic and slightly hydronephrotic

Method C. Uretero-Ureterostomy: In Experiments 19, 20, and 21 the animals died the second, third, and fourth days, respectively, after operation, of peritonitis from urinary leakage. In Experiment 22 the

Fig. 41 (Series III, Group 3, Experiment 5 [B 936]).—End-to-end anastomosis of the right ureter; fifty-six days' duration; slight constriction and dilatation of the right ureter, slight hydronephrosis of the right kidney; left kidney normal.

Fig. 42 (Series III, Group 3, Experiment 15 [C 131]).—Cuff anastomosis of the right ureter, eighty-one days' duration; slight dilatation of the right ureter; no stricture; right kidney normal; left kidney normal.

animal was killed the twenty-fifth day. At necropsy it was found that the anastomosis had healed perfectly, apparently without urinary leakage. The anastomosed ureter was dilated from partial constriction at the point of implantation and its kidney slightly atrophied. The recipient ureter was slightly dilated above the point of anastomosis, but the kidney appeared to be normal (Fig. 45).

Fig. 43 (Series III, Group 3, Experiment 10 [C 46]).—Cuff anastomosis of the right ureter, forty-three days' duration; partial constriction and dilatation of the right ureter; slight hydronephrosis with atrophy of the right kidney; left kidney normal.

From these experiments it seems that in the dog, cuff anastomosis is the method of choice as in only one case leakage of urine occurred, and that peritonitis resulting from urinary leakage is the most frequent cause of failure and death in anastomosing ureters.

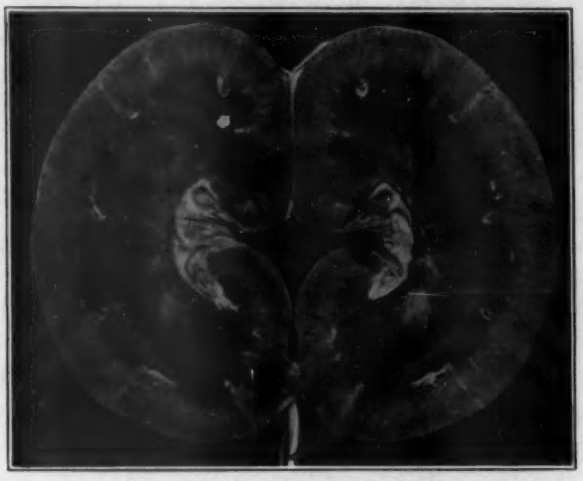

Fig. 44 (Series III, Group 3, Experiment 8 [C 119]).—Cuff anastomosis of the right ureter, eighteen days' duration; slight constriction and dilatation of the right ureter; right kidney normal.

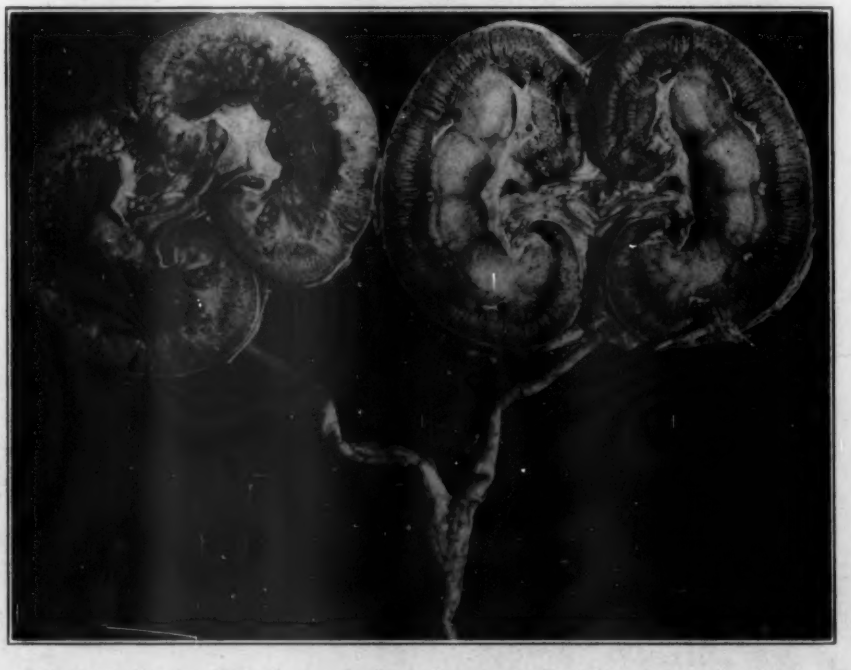

Fig. 45 (Series III, Group 3, Experiment 22 [C 48]).—Transplantation of the left ureter into the right, twenty-five days' duration; partial constriction and dilatation of left ureter with slight hydronephrosis and atrophy of the left kidney; dilatation of the right ureter above the anastomosis; right kidney normal.

SERIES IV. THE EFFECT OF DECAPSULATION OF THE KIDNEY

Great variations have been obtained in the results by experimental decapsulation of the normal kidney, particularly in the distribution of the blood vessels that are formed to repair the injury. The capsule is rapidly formed with an increase in the connective tissue of the cortex. There is still some controversy over the derivation of the new capsule and the distribution of the new blood supply. Emerson,[13] in 1903, after twenty experiments on dogs, concluded that the kidney forms a new capsule with marked vascular connections with the surrounding viscera, but not with the fatty capsule of the kidney, and that bands of connective tissue penetrate the renal parenchyma, simulating a diffuse nephritis. Johnson,[14] in 1903, from experiments on fifteen dogs, concluded that the kidney forms a new capsule and that there is round-cell infiltration of the cortex, but no anastomosis between the renal and peritoneal blood channels. Gifford,[15] in 1904, from experiments on the normal kidney of rabbits, found that a new very vascular capsule is formed after decapsulation, but that these new vessels do not anastomose with the branches of the renal artery of the cortex. Hall and Herxheimer,[16] working with rabbits, observed the formation of a new vascular fibrous capsule, but very few new blood channels between the kidney and the adherent tissues. Siter,[17] in 1912, from two series of experiments on cats and dogs, in two stages, found that a new capsule forms from the omentum and that a collateral circulation is established in ten days which is capable of maintaining the kidney function properly when the renal vessels are tied off.

Group 1. Decapsulation of the Kidney and Wrapping It in Omentum (Thirteen Experiments).—These experiments were undertaken for the purpose of determining (1) whether a new capsule would form; (2) whether the capsular circulation would be increased or decreased; (3) whether the branches of the renal artery and the arterial capsular blood vessels would anastomose, and (4) whether changes are produced

13. Emerson, H., and Meltzer, S. J.: Studies on the Capsule of the Kidney, Tr. Assn. Am. Phys. **18**:192-196, 1903.

14. Johnson, H. A.: Results of Decapsulation of the Kidney. A Study of Changes Noted in the Renal and Peripheral Tissues of Dogs After Decapsulation, Ann. Surg., **37**:592-601, 1903.

15. Gifford, N. H.: Experimental Decapsulation of the Kidneys, Boston M. & S. J. **151**:37-40, 1904.

16. Hall, I. W., and Herxheimer, G.: Experimental Nephritis Followed by Decapsulation of the Kidney, Brit. M. J. **1**:819-822, 1904.

17. Siter, E. H.: Results of Experiments on Kidneys, with Special Reference to Decapsulation and Establishment of Collateral Circulation, Surg., Gynec. and Obst. **15**:702-706, 1912.

in the renal parenchyma. Other points in relation to the decapsulation of diseased kidneys have not been completed.

The operative procedures were the same as those in the other series up to the point of exposing the kidney. In the majority of instances both layers of the fibrous capsule of the kidney were removed, with care

TABLE 10.—SERIES IV: THE EFFECT OF DECAPSULATION OF THE KIDNEY
Group I: Decapsulation of the Kidney and Wrapping It in Omentum
(Thirteen Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Decapsulation of Kidney and Wrapping in Omentum	Decapsulation of Kidney	Necropsy	Condition of Cortex	Formation of New Capsule	Increase in Capsular Veins Observed Macroscopically	Decrease in Capsular Veins Observed Macroscopically	Increase in Connective Tissue in Cortex
1 (124)	B793	2/19/17	353	Left	.....	53	.....	+	..	+	++
2 (286)	B900	3/24/17	203	.....	Right	539	.....	+	..	+	++
3 (591)	C114	8/24/17	169	.....	Right	58	.....	..	..	+	++++
					Left	...	.....	+	..	+	++
4 (543)	C 82	8/ 3/17	113	Right	Left	675	.....	Right	+	..	++
								Left			
5 (220)	B885	3/12/17	70	.....	Right	333	.....	+	..	+	++
6 (387)	B984	5/ 7/17	51	.....	Right	398	.....	+	..	+	++
7 (398)	B985	5/ 7/17	46	.....	Right	387	.....	+	..	+	++
8 (261)	B882	3/19/17	42	.....	Right	293	.....	+	+	+	++
9 (542)	C 81	8/ 3/17	17	Right	Left	489	.....	Right	..	+	++
10 (538)	C 77	7/30/17	17	Right	Left	480	.....	+	+	..	+
11 (98)	B768	2/10/17	7	Left	.....	77	Left, congested				
12 (535)	C 74	7/30/17	3	Right	Left	447	Left, congested; right, not congested				
13 (537)	C 76	7/30/17	2	Right	Left	446	Right, slightly congested; left, congested				

TABLE 11.—SERIES IV: THE EFFECT OF DECAPSULATION OF THE KIDNEY
Group 2: Decapsulation of the Kidney and Wrapping It in Omentum and Ligation of the Renal Artery or Branches of the Renal Artery (Seven Experiments)

Experiment	Animal	Date of Operation	Duration of Experiment, Days	Decapsulation of Kidney and Wrapping in Omentum	Ligation of Renal Artery	Ligation of One Branch of Renal Artery	Necropsy	Formation of New Capsule	Anastomosis of Renal and Capsular Arteries
1 (273)	C444	4/29/18	526	Right	.....	Right	404	++	
2 (99)	B760	2/10/17	16	Left	Left	.....	90	+++	
3 (53)	B742	1/27/17	10	Left	Left	.....	53	+	0
4 (398)	C529	6/17/17	348	Right	.....	Right	261		
				Left	.....	Left	...	++	0
5 (265)	C438	4/22/18	325	Right	.....	Right	93	++	0
6 (364)	C505	6/ 3/18	38	Right	.....	Right	347		
				Left	.....	Left	...	++	0
7 (235)	C412	4/ 4/18	15	Right	.....	Right	220	+	0

Fig. 46 (Series IV, Group 1, Experiment 7 [B 985]).—Decapsulation of the right kidney, wrapping in omentum, forty-six days' duration; formation of new dense, thick, fibrous capsule.

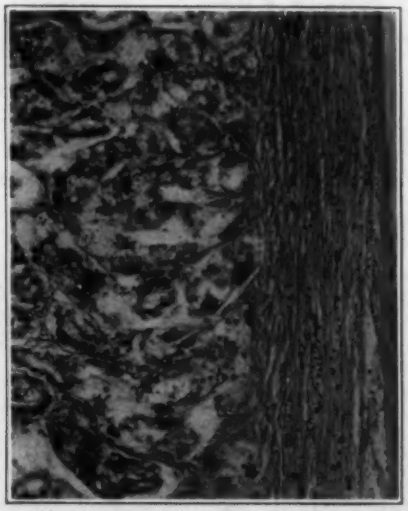

Fig. 47 (Series IV, Group 1, Experiment 2 [B 985]).—Section of capsule of kidney shown in Figure 46.

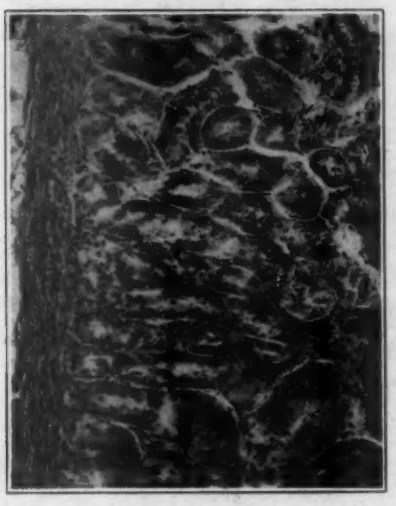

Fig. 48 (Series IV, Group 1, Experiment 4 [C 82]).—Decapsulation of right kidney, 115 days' duration; formation of new fibrous capsule closely associated with connective tissue of tubules.

Fig. 49 (Series IV, Group 1, Experiment 1 [B 793]).—Decapsulation of left kidney, wrapping in omentum, 353 days' duration; formation of a thick, fibrous capsule associated with the intratubular connective tissue.

to injure the renal parenchyma as little as possible. It is usually difficult to remove the inner, thin, reticular layer of the capsule because of its intimate association with the connective tissue surrounding the tubules of the cortex, There was considerable oozing of blood from the surface of the kidney after its capsule was removed; this was controlled by compression with gauze for about four or five minutes. The decapsulated kidney was then wrapped in omentum and replaced in the abdomen (Table 10 and Figs. 46 to 49).

The conclusions drawn from these experiments are that (1) the kidney forms a well marked new capsule in about seventeen days, (2) the interstitial tissue of the cortex increases, and (3) the newly formed capsule is more dense and fibrous and contains fewer (new) blood vessels than the normal capsule.

Group 2. Decapsulation of the Kidney and Wrapping It in Omentum and Ligation of the Renal Artery or Branches of the Renal Artery (Seven Experiments).—In two experiments the renal artery was ligated and the decapsulated kidney wrapped in omentum; and in five, one or more branches of the renal artery were ligated and the kidney decapsulated and wrapped in omentum (Table 11). These procedures had no effect on the production of atrophy, which indicates that the capsular vessels do not anastomose with the branches of the renal artery.

TUBERCULOSIS OF BONE

RESULTS OF A STUDY

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ST. LOUIS

INTRODUCTION

This study was made on the material collected during the treatment of fifty cases of bone tuberculosis. The patients were under treatment on the surgical service of the Barnes Hospital and the St. Louis Children's Hospital. The material obtained at operation was investigated in the laboratory of surgical pathology of the Washington University School of Medicine.

From the clinical standpoint, the cases used presented varying types of those manifestations usually associated with infectious bone lesions. Forty-two of the patients were adults; eight were children. In most cases, the symptoms and physical data made diagnosis of the tubercle bacillus as the etiologic factor a matter of no great difficulty. In some cases, diagnosis of tuberculosis was not made certain until the material placed in our hands by operation was sectioned and studied microscopically, and the confirmative evidence of animal inoculation was received. The clinical confusion between lesions due to syphilis and tuberculosis was a matter of especial concern. No cases were included in this group of fifty in which there remained any doubt as to the presence of syphilis as a causative factor.

It is not the purpose of this study to attempt to analyze the clinical pictures presented by this group of cases, but rather to call attention to the character of the lesions observed as seen under the microscope, the object in view being the simplification of our notions regarding the classification of the bone lesions due to tuberculous infection.

PATHOLOGIC MATERIAL

The focus of infection in the fifty cases studied was distributed about the bony framework of the body thus: spine, three cases; hip, eight cases; knee, sixteen cases; shoulder, six cases; ankle and tarsus, five cases; wrist, one case; elbow, two cases; trochanter major, one case; trochanter minor, one case; tibia, two cases; ulna, one case; humerus, one case; sternum, one case; malar bone, one case, and rib, one case: total, fifty cases.

Much has been written on the tendency of this disease to manifest itself in certain typical areas of the skeleton. So much is this the case

that an unusual location of the process will give rise to difficulty in diagnosis. In the cases studied in this group, there were several atypical foci of infection, such as might surprise one who had the conventional opinion that this disease occurs only at certain points. On the other hand, in the great majority of instances, the disease occurs and progresses along rather well established lines, well recognized clinically and pathologically. It is my belief that the more unusual forms of bone tuberculosis need a clearer clinical recognition.

CLASSIFICATION OF TUBERCULOUS BONE LESIONS

The pathologic changes that take place in bone tissue have been classified both from their macroscopic and microscopic appearances. Thus we recognize four distinct sets of changes and are schooled to regard these pictures as representative of clinical entities: (1) the encysted tuberculous lesion; (2) the infiltrating tuberculous lesion; (3) the atrophic tuberculous lesion, and (4) the hypertrophic tuberculous lesion.

Furthermore, it has long been the habit of those studying tuberculosis of the bone to include the bone lesions under one head and attempt to classify them as above, whereas the joint disturbances that follow tuberculous involvement of a joint area are separately classified and again regarded as distinct clinical entities. Thus we are schooled to recognize distinct clinical types of bone disease, as above, and joint disease, as, for example: (a) acute miliary tuberculous synovitis; (b) chronic tuberculous synovitis; (c) granulating or fungating tuberculous synovitis; and (d) fibrous tuberculous synovitis.

From the study of the material just mentioned, it seems worth while to attempt a simpler method of dealing with these various clinical and pathologic processes. The pathologic classification of an early day, long before the tubercle bacillus was known, when pathologists gave to us the rudiments of our present classification of disease, still has too firm a hold on the classification of osseous and articular disease. This may be due to lack of modern intensive study in this special field of pathology. In any event, we hang to the old names and old methods of classification. The skeletal structures that furnish the soil upon which tuberculous infection may become localized and develop are these: bone, of the cancellous and cortical types; periosteum; epiphyseal cartilage; articular cartilage; the epiphysis; the metaphysis; the diaphysis; bone marrow; the joint capsule; the ligaments, and the synovial membrane. Tuberculous infection gaining a foothold in any one or in several of these structures behaves in a manner which corresponds to the structure involved. In order that I may make clear my understanding of the changes wrought in the tissues as a result of tuber-

culous infection, I shall take up the material from the point of view of the particular tissue involved. There is no warrant, pathologically or clinically, to consider these lesions from the standpoint of contrasted bone or joint involvement. In most instances in this series of fifty cases, joints were involved in the process. In each and every instance, there was involvement of the bone. I find myself in accord with Nichols,[1] who was led to believe from his study of a similar group of cases that this disease is primarily a disease of the bone. I am not sure in what tissue the primary infection took place in all of these cases. I am sure that in all of them, the bone became the chief seat of the infection. Diligent search was made for evidence of primary synovial involvement, and for synovial involvement alone. No evidence was found of an instance of pure synovial tuberculosis. On the other hand, there is much evidence to show how the primary focus of disease located in the bone progresses to involvement of most of the intra-articular and extra-articular structures, as well as how it spreads in the bone tissue itself.

PART I. BONE TUBERCULOSIS WITH JOINT INVOLVEMENT

First I shall consider the cases in which the disease was apparently localized in the cancellous ends of the long bones and in which, through natural sequence, the adjacent joint or joints became diseased. This subgroup constitutes forty-one of the fifty cases.

In this group we have also the involvement of not only the cancellous bone to consider, but also such structures as the articular cartilage, the synovia, the joint capsule and ligaments. Case 1 is typical.

CASE 1 (Figs. 1, 2, 3, 4 and 5).—In this case a diagnosis of tuberculosis of the shoulder was made on clinical findings. The head of the humerus was excised, a specimen of which is shown in Figure 1. Here there was evident erosion of the joint cartilage; the joint surface was extensively involved, the cartilage being eroded at the margins and on the center of the surface, where there is a depression. Macroscopically, this joint surface inclined us to the belief that we had discovered a case of chronic tuberculous synovitis. After the entire head was decalcified and a section made of the specimen in the midfrontal plane of the humerus, the original focus became apparent (Fig. 2). The macroscopic appearance of the bone trabeculae in the sections cut would justify the diagnosis of atrophic tuberculous lesion. The microscopic sections at the area of the focus would justify the assumption that we were dealing with the infiltrating tuberculous lesion of Nélaton (Fig. 3). Here we have tuberculous granulation tissue surrounding the trabeculae, which are being broken down in a rapid manner by osteoclasts and caseation is spreading rapidly. The attempt in the marrow to fight off the disease is lacking, there being very little fibrous reaction.

1. Nichols, E. H.: Tuberculosis of Bones and Joints, Tr. Am. Orthop. Assn. **11**:383, 1898.

Case 1: Figure 1.

Case 1: Figure 2.

Case 1: Figure 3.

Case 1: Figure 4.

Here also we have erosion of the cartilage of the joint from below, and a "break through" into the joint cavity by tuberculous granulations (Fig. 4).

Finally, Figure 5 shows the thickened synovial membrane, with extensive tuberculous involvement.

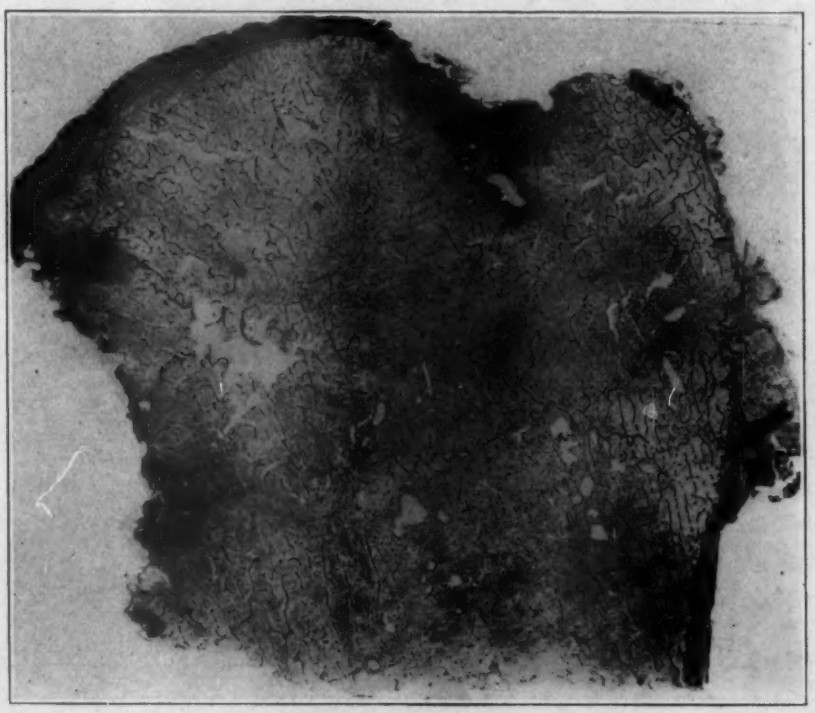
Conclusions.—A search through the various tissues studied in this case will reveal pictures corresponding to most of the classifications now used in attempting to group tuberculous bone lesions. Figure 2, which is a slightly enlarged photograph of a section cut through the head, reveals extensive atrophic changes in the bone. I believe this to be disuse atrophy, as bones not used will show similar change in size and number of the trabeculae of the cancellous bone.

Case 1: Figure 5.

At the site of tuberculous involvement, microscopic search will reveal rapid involvement and destruction of bone elements, the cartilage shows erosion and breaking through, and the synovial membrane is thickened and tuberculous. There is: (1) tubercle formation; (2) caseation; (3) atrophic changes; (4) cartilage destruction; (5) infiltration changes; (6) synovial tuberculosis and (7) practically no effort at repair: a typical picture of tuberculosis of the bone with secondary joint involvement.

After two years of clinical quiescence, an operation was performed in this case for flail shoulder. The portions of bone removed from the end of the shaft showed typical features of tuberculosis of bone. Here the disease process had extended to the shaft of the bone and was characterized by proliferative or "hypertrophic" changes.

CASE 2 (Fig. 6).—*Tuberculosis of Shoulder Joint.*—This case, though not so typical in all its details of the history of bone tuberculosis with subsequent joint involvement as is Case 1, is, nevertheless, quite characteristic of some of the points I wish to emphasize. Figure 6, a photomicrograph of the upper end of the humerus, shows clearly the marked atrophic changes in the trabeculae of the cancellous bone, i. e., atrophic type of tuberculosis. In numerous areas, there are seen fields of an infiltrating type of tuberculosis (Fig. 7). Again the breaking through of the joint cartilage is beautifully shown in Figure 8.



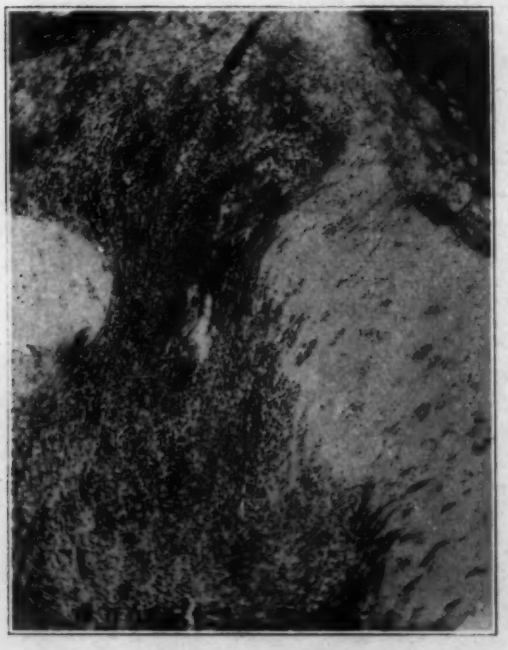
Case 2: Figure 6.

Conclusions.—Here we have atrophic and infiltrating types and the involvement of the joint with extensive cartilage erosion and tuberculosis of the synovial membrane. The atrophic change is due to disuse.

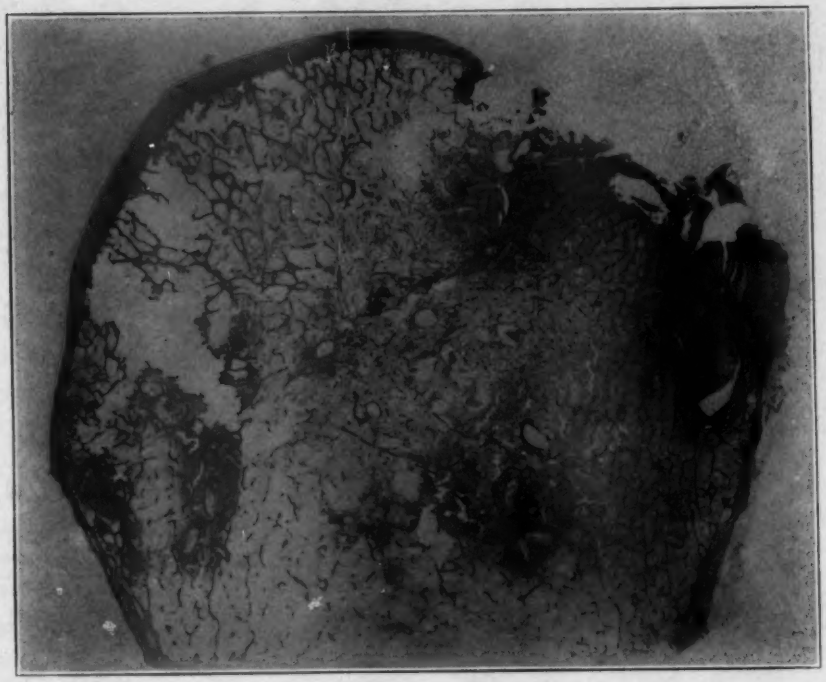
CASE 3 (Fig. 9).—*Tuberculosis of Shoulder.*—Here we see again the extensive atrophy of the cancellous bone of the upper end of the humerus, with cartilage erosion (Fig. 10), and tuberculosis of the synovial membrane. There is also evidence in many fields of the infiltrating type of tuberculosis, with trabeculae that have become necrotic, caseation, and very poor evidence of attempted repair by fibrous tissue formation.

Conclusions.—In the same specimen, we have the various pictures of tuberculous involvement of certain structures. The atrophic change is due to disuse.

Case 2: Figure 7.



Case 2: Figure 8.



Case 3: Figure 9.

Case 3: Figure 10.

CASE 4 (Figs. 11 and 12).—In this case of hip disease of many years' duration, sections through the head of the femur show various pictures of the disease process.

Figure 11 shows marked atrophic and infiltrating changes. The trabeculae are being rapidly destroyed by osteoclasts, low vascularity and caseation. Figure 12, on the other hand, shows power of repair; the marrow spaces are filled with fibroblasts, increased vascularity, and the trabeculae are surrounded by osteoblasts, and definite new bone formation.

Conclusions.—Destruction and healing are going on side by side in tuberculous bone disease.

CASES 5 AND 6 (Figs. 13 and 14).—In these cases of hip joint tuberculosis the bone which was excised shows characteristic areas of active tuberculous disease with destruction of trabeculae and at the same time a general atrophy of the cancellous bone. Figures 13 and 14 show characteristic involvement of the joint cartilage. In Figure 13, there is an area of intense "infiltrating" tuberculosis of the cancellous bone directly under the joint cartilage. The cartilage shows by its appearance of "buds" that granulation tissue is pushing through from below. In Figure 14, these "buds" in the cartilage are well shown. In both these cases there was involvement of the synovial membrane.

Brooks and I[2] have carefully described this behavior of the joint cartilage when the cancellous bone becomes the seat of an infectious process. Its behavior does not vary greatly with the type of infectious agent.

CASE 7 (Figs. 15, 16, 17, 18 and 19).—*Tuberculosis of Knee.*—A coal miner, aged 53, appeared at the clinic with evident tuberculosis of the knee. Excision was advised, but operation was refused. A plaster-of-Paris cast was applied, and crutches and a high shoe were used. He was treated conservatively. After eleven months, he returned with the knee much worse. Amputation was advised, but refused. Excision was allowed. The knee joint was excised, and extensive involvement of all tissues was found. Healing took place; but tuberculosis advanced in new areas. The patient submitted to amputation at the end of nine months, but died of general tuberculosis several months later.

As is often the case in surgical treatment, especially of cancer and tuberculosis, the surgeon was a step behind the advance of the disease.

Gross Pathology, After Excision, First Operation.—The tissue consists of the femoral condyles, the head of the tibia, and the patella. There is an area of total bone destruction on the lateral surface of the condyle about 1 cm. in diameter and depth, with typical caseous tuberculous granulation tissue. A similar cavity is found in the head of the tibia also, which communicates with the joint cavity through an opening at the base of the crucial ligaments. There is extensive destruction of the margins of the joint cartilages; those on the joint surface of the patella are completely undermined. The joint capsule at the margins of the patella shows numerous miliary tubercles in granulation tissue.

Gross Pathology, After Amputation, Second Operation.—The specimen received is the left leg amputated at the lower third of the femur. After fixing the leg in liquor formaldehydi it was cut through with a saw in the midline, longitudinally. There was no union between the femur and tibia.

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2. Allison, N., and Brooks, B.: Ankylosis, Surg., Gynec. & Obst., November, 1914.

Case 4: Figure 11.

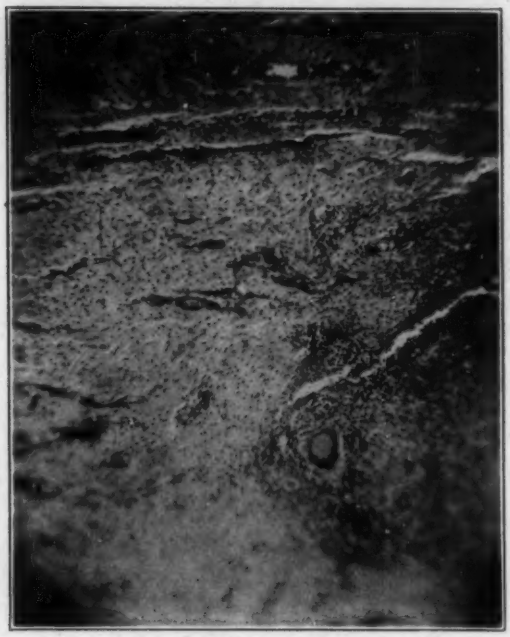
Case 4: Figure 12.

Case 5: Figure 13.

Case 6: Figure 14.

Case 7: Figure 15.

Case 7: Figure 16.



Case 7: Figure 17.

Case 7: Figure 18.

Both the upper tibia and the lower femur are necrotic. A sinus tract extends from the knee down to the middle third of the leg, along the posterior muscle layers.

Microscopic study of the various tissues in this case shows extensive tuberculosis. Figure 15 shows an area of rapid bone destruction with the trabeculae becoming necrotic in a mass of granulation tissue with caseation. Figure 16 shows the joint cartilage resting on a mass of tuberculous granulations. Figure 17 shows extensive tuberculosis in the joint capsule. Figure 18 shows extensive tuberculosis in the wall of the sinus. Figure 19 shows a section through the tibial head with the periosteum. Here there is evident new bone formation. (The new bone formation will be discussed in Part II.)

Conclusions.—Aside from the clinical features of this case, the bare recital of which places enough emphasis on their significance, the case presents the

Case 7: Figure 19.

ultimate results in bone tuberculosis of extension from bone focus to joint, and to all the tissues, i. e., bone cartilage, synovial membrane, capsule, ligaments, muscle layers and skin.

Tuberculous lesions of all described types may be found in these tissues.

Case 8 (Fig. 20).—*Tuberculosis of Spine.*—A laborer, aged 37, after an injury to the spine, developed typical Pott's disease, kyphosis developing at the fifth and sixth dorsal vertebrae. He became completely paraplegic, with no sensation below the ribs. Under the impression that an exudate might be pressing on the cord, laminectomy was performed. He made a good recovery, with no improvement. The excised laminae and spinous processes were sent to the laboratory.

Gross Pathology.—The tissue consists of several pieces of bone, some of which have muscles attached. The pieces range from 1.5 by 0.5 cm. to smaller particles. No granulation tissue was received.

Microscopic Pathology.—Figure 20 is a section through the spinous process. Very definite tuberculous destruction of bone with tubercles and caseation is seen.

Conclusions.—It is generally assumed that Pott's disease, or vertebral tuberculosis, is localized in the bodies of the vertebrae. It is usually so localized; but it may involve by extension the laminae and spinous processes.

Case 8: Figure 20.

Case 9.—*Tuberculosis of Tarsal Bones.*—Figure 21 shows the process of healing after a tuberculous invasion of the cancellous bone. Here fibrous marrow has developed; the spaces between the trabeculae are occupied by fibrous tissue.

Case 10.—*Tuberculosis of Shoulder.*—Figure 22 shows the fatty fibrous appearance of a healing bone lesion. The osteoblasts about the trabeculae may be noted also.

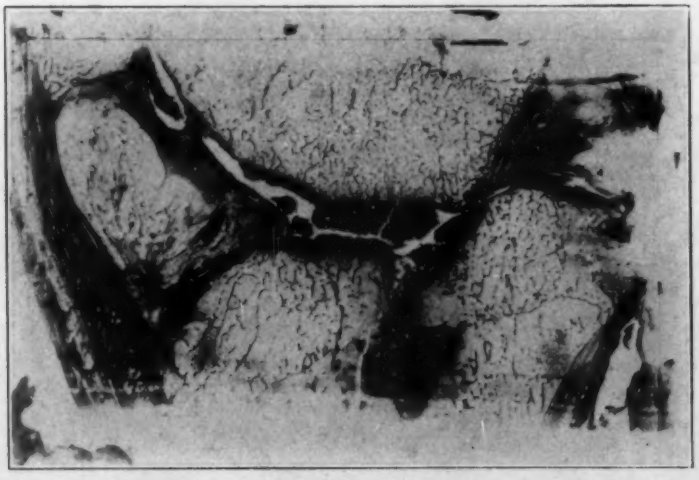
Case 11.—*Tuberculosis of Knee.*—Figure 23 is a low power photomicrograph of a break through the joint cartilage following bone involvement in the cancellous bone of the tibia.

Case 12 (Figs. 24, 25, 26, 27 and 28).—*Tuberculosis of Knee.*—Figure 24 is a photomicrograph of the specimen. It shows the gross changes that were observed. The articular surfaces of the femur, the tibia and the patella are covered with a thick granulation tissue. Very little cartilage remains, and that in small islands; but the original focus of bone involvement is shown in the tibial head, and is shown in direct communication with the joint cavity.

Case 9: Figure 21.

Case 10: Figure 22.

Case 11: Figure 23.

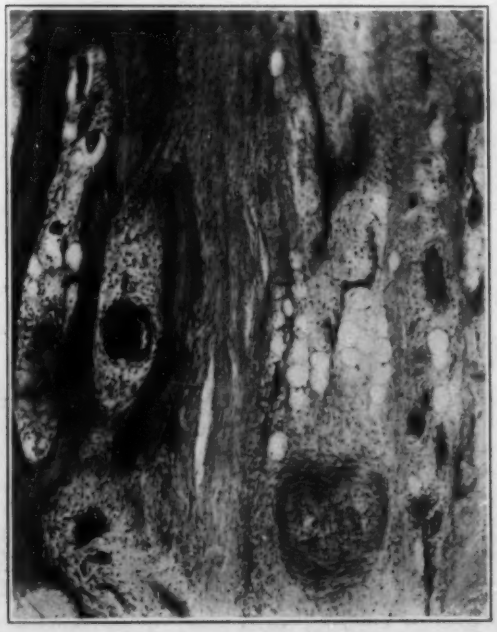


Case 12: Figure 24.

Case 12: Figure 25.

Case 12: Figure 26.

Case 12: Figure 27.



Case 12: Figure 28.

The picture, judged from the gross findings, might be labeled chronic tuberculous synovitis. Microscopic study of the sections reveals extensive tuberculous involvement of cancellous bone (Fig. 25), marked atrophy of bone (Fig. 26), extensive tuberculosis of the joint capsule (Fig. 27), and involvement of the periosteum with proliferation of new bone on the tibial surface (Fig. 28).

Conclusion.—We have here a typical picture of joint involvement occurring with bone tuberculosis. The microscopic findings reveal in the specimen areas that would correspond to most of the classifications of the lesions of the disease. The proliferation of new bone noted in Figure 28 will be discussed in Part II.

SUMMARY OF PART I

The material thus far selected, with three exceptions, reveals the well recognized classical picture of skeletal tuberculosis. The clinical characteristics of this picture are the onset, indicating bone involvement, and the gradual extension, indicating joint involvement. Pathologically, we have in this group the classical pictures also of bone and joint tuberculosis, a slow process with bone destruction, poor healing ability, and this by fibrous tissue, joint destruction with abscess formation, and ankylosis, if the diseased person survives the process sufficiently long. The three exceptions are the pictures of proliferation discovered in the cases in which the disease process had progressed far enough from the cancellous ends of the bone to reach the region where periosteum is found. This tissue responds to infection by rapid proliferation and well illustrates in three instances the point I wish especially to emphasize: The nature of the tissue in its reaction to infection determines the anatomic pathologic condition which results. The results of the search through this material lead to the conclusion that bone tuberculosis has its origin, in the great majority of instances, in the cancellous bone, and its extension to the neighboring tissues with their individual characteristics of reaction to infection explains the various types of the disease.

PART II. BONE TUBERCULOSIS WITHOUT JOINT INVOLVEMENT

It is essential to understand that I regard what is to follow as a report of atypical tuberculous lesions. As stated before, the typical lesion of skeletal tuberculosis is that of bone involvement with joint involvement, going hand in hand. I believe the primary lesion to be osseous, because I have not discovered a primary lesion in other tissues. In all cases, the joint changes and the bone changes are, as a rule, closely associated.

In this portion of the study, I have included those cases that presented bone disease without joint involvement. I do not believe with Stiles and Fraser that this type of lesion is common. At least, it is not so in America. I do wish to point out that Stiles' and Fraser's observa-

tions are correct, and to add my testimony to the truth of Fraser's statement that "hypertrophic" tuberculous lesions do exist. In Fraser's[3] work, "Tuberculosis of the Bone and Joints in Children," he describes a type of bone tuberculosis which he calls "the hypertrophic tuberculous lesion." After a careful description of this lesion as a type, he states in a footnote that he believes that here we are dealing with a syphilitic lesion which has secondarily become infected with tuberculosis. He was led to this statement by the fact that the cases he has studied had not been definitely determined as nonsyphilitic. I wish to show that in all probability, most of his work on what he calls the "hypertrophic" type of tuberculous infection was correctly observed. Before this, in this study, I have cited three instances in which tuberculosis of bone was characterized by new bone formation. I have pointed out that the reason for this is that the infection had gained a foothold in the periosteal region of the bone, and that the periosteum reacts to infection by marked proliferation.

Fisher and I[4] have described in some experimental work on bone tuberculosis the lesions that take place when the subperiosteal region in dogs' bones was infected with tuberculosis. It showed that tuberculosis could develop subperiosteally as well as in the cancellous bone. Ely has deduced a theory at variance with this experimental fact. His theory also is at variance with the observations of Fraser on the so-called "hypertrophic tuberculous lesion." A study of the cases in this group will throw some additional light on this discussion.

CASE 13 (Figs. 29, 30, 31, 32, 33 and 34).—A child, aged 5 years, presented peculiar bone lesions resembling chronic pyogenic osteomyelitis. The Wassermann reaction was negative; the tuberculin test positive; the right ulna, left ulna, and middle of the shaft of the left tibia were involved. Portions of the diseased shafts were removed by operation.

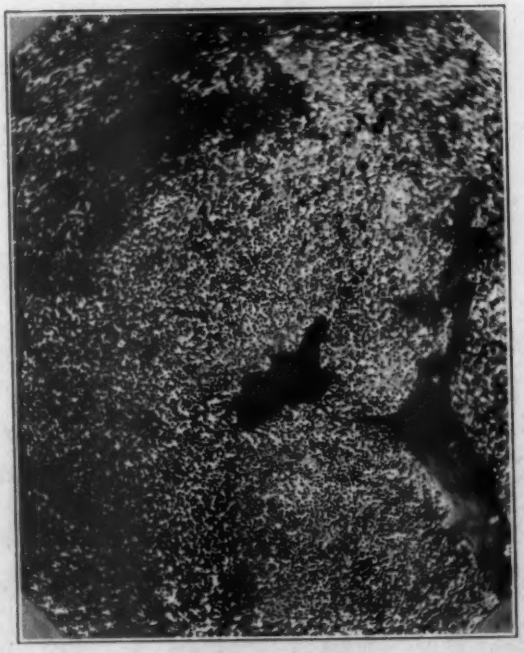
Gross Pathology.—Specimens consist of several fragments of bone and soft tissue. One labeled "new formed subperiosteal bone" consists of bone fragment, 1 cm. in diameter, and 2 mm. in thickness. Another specimen is a portion of the hard cortical bone of the shaft. A third, labeled "medullary cavity," consists of ragged soft tissue adherent to cancellous bone. One or two small white bodies resembling tubercles are seen in this tissue.

Microscopic Pathology.—Figures 29 and 30 show tuberculous lesions in the bone similar in all respects to rapid destruction of cancellous bone by tuberculosis, especially in Figure 30, in which there is a caseating mass of granulation tissue surrounding necrotic trabeculae. In Figure 31, we observe a mass of new bone, rapidly proliferating in close proximity to a mass of tuber-

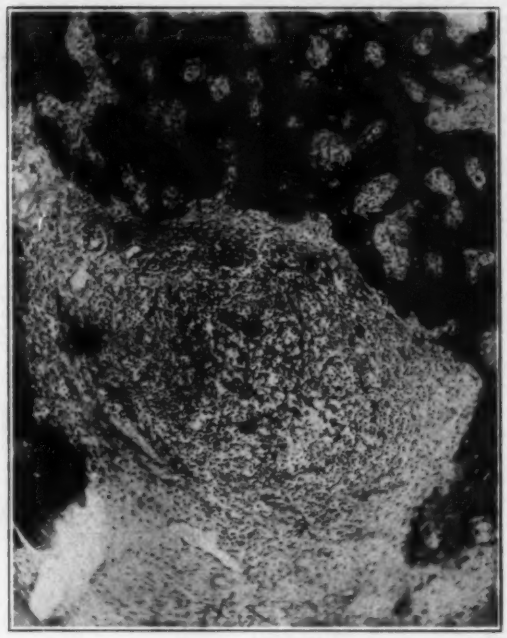
3. Fraser: Bone and Joint Tuberculosis in Children, New York, The Macmillan Company, 1914, p. 26.

4. Allison, N., and Fisher, R. F.: Experimental Bone Tuberculosis, Am. J. Orthop. Surg. **14**:631 (Nov.) 1916.

Case 13: Figure 29.



Case 13: Figure 30.



Case 13: Figure 31.

Case 13: Figure 32.

Case 13: Figure 33.

Case 13: Figure 34.

culous granulations. In Figure 32, we have subperiosteal new bone formation, with very active new bone growth. The tissue is fibrous and of increased vascularity.

In Figure 33, to which I wish especially to call attention, we have the compact bone of the shaft of the tibia, and located in it is a tuberculous focus.

In Figure 34, we have a beautiful picture of periosteal tuberculosis, with marked bone proliferation. Of especial significance in these observations is the fact that this child was proved, as far as clinical tests go, to be syphilis negative, and the guinea-pigs inoculated with the material proved tuberculous. Here, then, we have definite new bone proliferation alongside of bone destruction, associated with the activity of the tubercle bacillus. The occurrence of the pure focus of tuberculosis in the compact bone of the shaft shown in Figure 33 offers positive proof that a tuberculous lesion may occur in compact as well as in spongy bone. It is worthy of note that although some of the process is distinctly of the character of "hypertrophic" tuberculosis, destructive lesions are abundant in the tissue.

CASE 14 (Figs. 35 and 36).—*Tuberculosis of Ankle Joint.*—Figure 35 is a slightly enlarged photomicrograph of a frontal plane section of the tibia, just at the malleoli. There is very evident bone atrophy; the trabeculae are small and have lost their normal architectural arrangement. At the side is a large tuberculous abscess. Here there is caseation and rapid bone destruction.

Figure 36 is a photomicrograph of a section from just above the abscess through the periosteum and cortex of the tibia. Here we see rapid and extensive new bone formation as a reaction to tuberculous involvement.

CASE 15 (Fig. 37).—*Tuberculosis of Knee.*—Here we have extensive and rapid bone proliferation in a section through the periosteum of the tibia, in which the knee was extensively involved in tuberculous disease.

CASE 16 (Fig. 38).—*Tuberculosis of Lesser Trochanter.*—A negro, aged 45, for four months had had a lump in the groin, had become unable to walk, and had been confined to bed five weeks. His thigh was swollen. The roentgen ray showed a mass near the lesser trochanter. He was operated on.

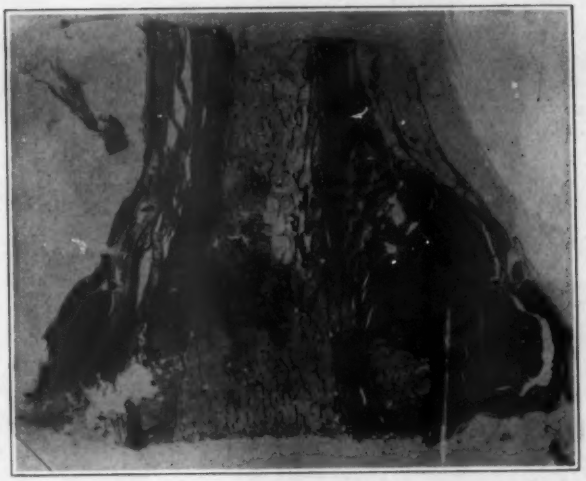
Gross Pathology.—The tissue consists of bone from the region of the lesser trochanter and pus from the abscess cavity. The bone is slightly spongy and is 4 by 3 by 2 cm. in size.

Microscopic Pathology.—Sections of this exostosis show newly formed bone in a mass of granulation tissue with definite tubercle formation.

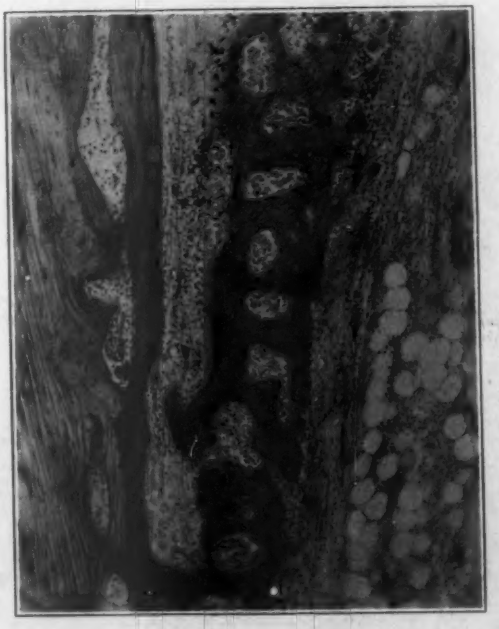
A guinea-pig inoculated with the material showed extensive peritoneal tuberculosis. Figure 38 is a photomicrograph of the granulation tissue in this case. It is definitely of tuberculous character; but there might remain some doubt were it not for the positive guinea-pig reaction. Here we have a pure tuberculous exostosis of a long bone.

CASE 17 (Figs. 39, 40, 41 and 42).—*Tuberculosis of Shaft of Humerus.*—A girl, aged 11 years, had had a swelling about the left elbow for five months. The roentgenogram showed large cauliflower-like expansion of the lower third of the shaft of the humerus. The diagnosis was periosteal sarcoma. Amputation was advised but refused by the child's parents. The lower 15 cm. of the humerus was excised. A bone graft was substituted. Subsequent history showed good recovery.

Macroscopic Pathology.—Figure 39 is a drawing of the gross specimen. The shaft at the site of amputation appears normal. There is fusiform swelling of bone. The tumor seems to be some type of subperiosteal growth.

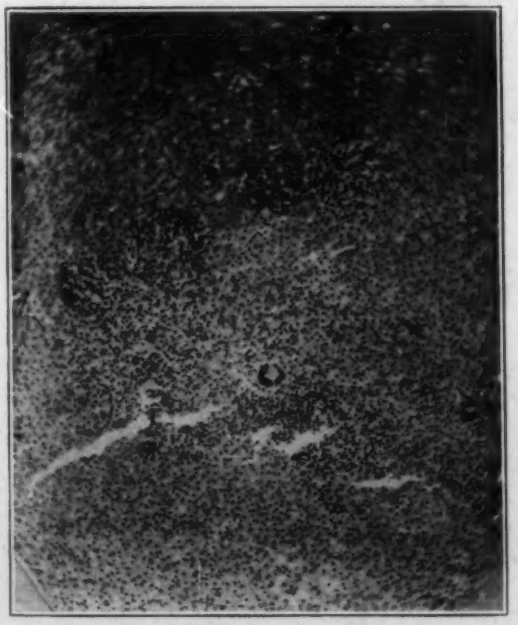


Case 14: Figure 35.



Case 14: Figure 36.

Case 15: Figure 37.



Case 16: Figure 38.

Case 17: Figure 39.

Case 17: Figure 40.

Case 17: Figure 41.

Microscopic Pathology.—Sections show the tissue to be inflammatory. There are large areas of new bone formations (Fig. 42); the narrow spaces of the newly formed bone are filled with dense fibrous tissue. The margins of the tumor show an active inflammatory process. There are areas of necrosis with giant cells (Fig. 40) and with typical tubercles.

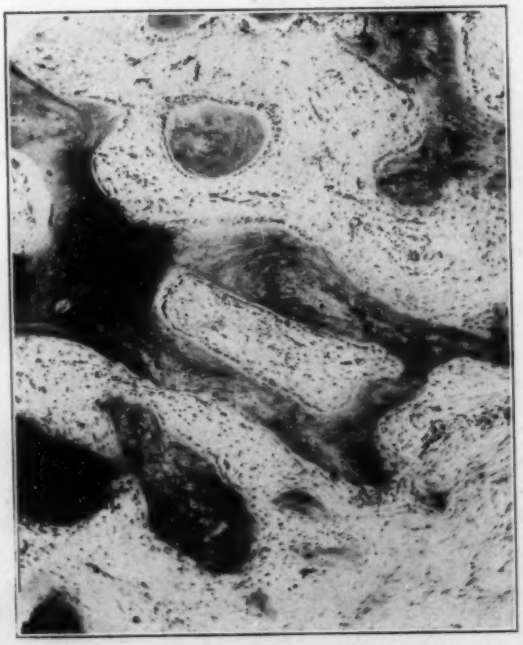
Figure 41 shows fields of less active destructive process with fibrous elements more evident than in Figure 40.

It is to be noted that this case was not proved to be tuberculous by animal inoculation. The child was syphilis negative. The subsequent history would also be against syphilis. I am inclined to believe that here we have a case of pure subperiosteal tuberculosis, with hypertrophic bone changes as the predominating process. There are, however, in the specimen, many areas of typical rapid tuberculous destruction of bone. This case is similar to those so well described by Fraser.

Case 17: Figure 42.

Case 18 (Figs. 43 and 44).—*Tuberculosis of Tarsus.*—The healing of the tuberculous bone lesion is accomplished by the formation of fibrous tissue. Around the area of disease, all tissues tend to become fibrous. The marrow loses its cellular character and becomes fibrous or fatty-fibrous. In Figures 43 and 44, this process is well shown. In Figure 43, the inflammatory process is still active, but to be noted are the increased amount of fibrous tissue and new bone cells. In Figure 44, the process is very well advanced. The osteoblasts about, and the greatly increased number of bone cells in, the trabeculae, also the dense fibrous tissue filling the marrow space are to be noted.

Case 18: Figure 43.



Case 18: Figure 44.

SUMMARY OF PART II

The material grouped here has as its characteristic the involvement of the shafts of the bones away from the epiphyses. It is characterized by a marked tendency to bone proliferation, and might be regarded as "hypertrophic" in type. It is to be observed, however, that the picture of proliferation is accompanied in each specimen by areas that have typical destructive lesions; in consequence, we should not lose sight of the fact that tuberculous lesions behave in a manner directed by the tissue reaction to infectious processes.

When the tubercle bacillus invades tissues which in their reaction to infection readily produce new bone, the lesion observed has as one of its characteristics *new bone formation*.

When the tubercle bacillus invades tissues which in their reaction to infection do not readily produce new bone, the lesion observed has *not* as one of its characteristics new bone formation.

In all instances in this study in which tuberculous bone lesions were observed, there was both bone destruction and bone proliferation. When cancellous bone was involved, destruction predominated. When compact bone was involved, proliferation predominated.

CONCLUSIONS

Tuberculosis may involve any portion or tissue of the bony framework of the body.

Tuberculosis is by far more frequently localized in the ends of the bones, and as a consequence, generally involves a joint or joints.

The pathologic process is to be regarded as not essentially different in its manifestations wherever it may occur. If tissues are involved that possess the property of rapid proliferation when infected, this process will be observed when the tubercle bacillus is the agent. If tissues are involved which do not rapidly proliferate under infection, destruction will be observed when the tubercle bacillus is the agent.

It is cumbersome, confusing, and in a sense wrong, to describe the process of tuberculosis separately, as it affects bone tissue of various types and joint structures. It is all one and the same. The variations are due only to the characteristics of the tissue infected.

It is also unwarranted to classify this disease as to the type of reaction observed. I believe that search will reveal most types of process in practically any well established lesion. I mean by this, that I am opposed to the terms employed in the older literature as classifications, such as infiltrating, atrophic, caseous and hypertrophic tuberculosis of the bone. This is especially true of such descriptive terms as "chronic synovial tuberculosis" and "fungating" or "granulating tuberculous

synovitis." Here the observer has described one phase of a tissue reaction, as a pathologic and clinical entity.

My observations on this series of fifty cases incline me to believe with E. H. Nichols that the disease is primarily osseous.

I am also of the belief that the disease may occur more frequently than is generally believed in the regions of the skeleton away from the joints, and that this fact should be emphasized in the teaching of the characteristics of this disease.

Editorial Review

THE TREATMENT OF ACUTE *EMPYEMA*

The pleural and peritoneal cavities are similar in their embryology, physiology and pathology. The character and arrangement of their contents constitute an important difference, as does also the constitution of their walls. The mobile intestines, with their mesenteries, also the omentum, aid in localizing infective processes and hinder the establishment of effective drainage. The yielding abdominal wall normally keeps the peritoneal cavity a potential, instead of an actual, cavity, while in the chest it is the expanding of the lung which does the same thing for the pleura, the chest wall remaining rigid. As disease commonly impedes pulmonary expansion, it is much more common to have an actual, instead of a potential, pleural cavity, than to have such a condition in the peritoneum. When an intra-abdominal organ, such as the appendix vermiformis, becomes the site of an infective lesion, the diffusible toxins spread beyond the focus of infection and give rise to the phenomena of inflammation in the adjacent peritoneum. There is effusion of lymph, and an adhesive tumor forms, which commonly localizes the infection so that, unless interfered with by injudicious treatment or abuse, resolution takes place or an abscess forms. If the original infection is very virulent, there is no time for the development of protective inflammatory processes and wide-spread infection of the peritoneum results. Absorption of toxins may cause fatal poisoning or dissemination of microbes may cause pyemia or septicemia.

In pneumonitis, of whatever origin, the pleura commonly becomes affected in a manner entirely analogous to that in which the peritoneum is involved. One may look upon pleuritis secondary to lung disease as an attempt on the part of Nature to give the lung rest, and, by means of temporary or permanent adhesions, to limit the area of the pleural cavity which will be exposed to the escape of infective material from the lung.

In croupous or pleuropneumonia (lobar pneumonia), the pleuritis is commonly of the protective variety, and with the subsidence of the pulmonary disease, the pleuritis also disappears. If, however, sufficient infection has passed from the lung into the pleuritic exudate, a localized or extensive empyema results. In these cases, the empyema develops or becomes evident only when the pneumonia is either cured or in process of cure. The empyema itself is then the menace to life and demands treatment.

In the pneumonias, common during epidemics of influenza and other acute infective fevers, the virulence of the infective agent is such that the pleura has no time or has insufficient resisting power to go through the changes necessary for the formation of a barrier of protective inflammation. The condition is entirely like that found in the peritoneum in fulminating appendicitis or in acute perforation of the stomach, but, whereas in peritonitis from such causes as this, the primary lesions are very limited in extent and may commonly be extirpated or closed by operation, in pleuritis the causative pulmonary lesion is not susceptible of surgical removal or repair.

As might be expected in pleuritis following lobar pneumonia, the fluid effused is at first clear, then cloudy, and later it becomes thick creamy pus, containing masses of fibrinous material from the heavy croupous membrane so often formed on the pleura. In streptococcic empyema beginning during active pulmonary disease, the fluid, at first thin and dirty, has much less tendency to become a creamy pus. The pleural infection may appear on the side in which the lung is not involved, or with unilateral pneumonia, there may be bilateral empyema. Cases have been reported in which there has been a true empyema on one side and a sterile collection of clear or puslike fluid on the other. Complications are common, such as multiple abscesses of the lung or brain, nephritis, endocarditis, in fact, the usual phenomena of pyemia and septicemia.

As has already been noted, there is commonly recovery from the protective pleuritis as soon as the causative pneumonia has disappeared; but as in peritonitis, so also in pleuritis, this recovery may be accompanied by the formation of adhesions which may or may not be crippling. If an empyema has not been drained properly or early enough, the lung may fail to expand and obliterate the empyema cavity. This failure may be due to compression exerted by a thickening and contraction of the visceral pleura which result from Nature's efforts at healing, identical with the formation and contraction of scar tissue in any other locality. The lung itself may fail to expand because of atelectasis, or because of long compression during recovery from the pneumonitis, the reparative processes may have accommodated themselves to the diminished volume of the lung, and there is a state of fibrosis which is more or less stable.

INDICATIONS FOR TREATMENT

When empyema is present during the acute stages of pulmonary disease, one might at first think it proper to establish drainage in the hope (*a*) of lessening embarrassing pressure on the lung, and (*b*) of withdrawing large amounts of virulent toxins; but experience has

shown this to be fatally wrong. E. A. Graham [1] finds that in acute empyema, especially of streptococcic origin, there is a low vital capacity.[2] In the early stages, with cyanosis and air hunger, it is evidently difficult to obtain the tidal air which is now equal to the vital capacity; and even a small opening through the chest wall is fatal. In other words, when the acute pulmonary condition is such that the patient cannot inspire by a full effort more air than he could inspire in easy breathing, the tidal air and the vital capacity are equal, and any pneumothorax will decrease the quantity of air inspired.

When epidemics of influenza, measles, etc., invaded the training camps in 1917 and 1918, acute pneumonia and empyema promptly appeared. At first early operation was the rule, and the mortality was frightful (at Fort Riley, 61.2 per cent.). When late operation was adopted, the mortality fell to 26 per cent. and then to 7 per cent. (Stone's statistics, Fort Riley). The danger of early operation, that is, operation while the pneumonic process is active, was well known many years ago; but physicians and surgeons practicing in 1917 were accustomed to empyema following lobar pneumonia and obtained the best results from operation performed early as regards the empyema, but *late* as regards the pneumonia. This they called *early* operation, and they thought the earlier the operation was performed the better. They wrongfully applied the experience gained in treating one class of empyema to a totally different class.

Legendre [3] in a very practical manner divides patients with empyema into two classes: (1) those with "white dyspnea" in whom the dyspnea is moderate, the respiration rate being about 25 to 30 per minute. The pallor is due to toxemia. The pulmonary lesions are either extinct or are nearly well. In such cases, the beginning of the acute infection (influenza, measles, etc.,) dates back from twenty-six to fifty-eight days. The infective agents are various (staphylococci, streptococci, pneumococci, etc.). After operation, the fever subsides promptly, the dyspnea improves progressively, and recovery is the rule. (2) Those with "blue dyspnea" in whom the rate of respiration is from 45 to 50. There is marked cyanosis of the face and extremities. These symptoms are in proportion to the pulmonary and not the pleural lesions. Operation increases the dyspnea, has no effect on the fever and is generally promptly followed by death. According to Legendre, "Neither the nature of the microbe nor the precocity of the operation seems then to modify the prognosis of these purulent pleurisies. This seems to be

1. Graham, E. A.: Surg., Gynec. & Obst. **31**:60 (July) 1920.

2. Vital capacity is the volume of air which can be expelled from the lungs after a full inspiration.

3. Legendre, L.: Presse méd. **27**:22 (Jan. 16) 1919.

almost exclusively dependent on the condition of the subjacent lung and especially of the opposite lung. If the functional value of these is already defective because of extensive lesion, operation aggravates rather than ameliorates the situation." Graham and Legendre, approaching the subject from different angles and working in different countries, have thus come to identical conclusions.

PRINCIPLES OF TREATMENT

The first object of treatment is to keep the patient alive; the second is to obtain a return to perfect health, both functional and anatomic, as quickly and comfortably as possible. The first object must be sought by medical and dietetic treatment and by nursing. Good nutrition, good air and good elimination are essential. Palliative aspirations are often necessary. Vaccines do not seem to have been of much value, especially antistreptococcic vaccines. The treatment of the causative pneumonias belongs exclusively to the physician. Until the pneumonia is at least in process of cure, surgical intervention is almost always objectionable meddling. In the so-called "blue dyspnea," operation is always wrong. As soon as the pulmonary condition permits, provided the general condition of the patient does not forbid, surgical intervention becomes proper or imperative. The principles of surgical treatment are: (*A*) *drainage;* (*B*) *sterilization,* and (*C*) *lung expansion.* Every one is agreed on the necessity of carrying out these principles; the methods employed to carry them out are legion, and their merits are championed with enthusiasm or damned with cordiality.

DRAINAGE

When the empyema cavity is of very limited extent, it should be opened at any convenient point as indicated by roentgenograms and the exploring needle. Every one agrees that in all large empyemas the drainage should be established at the low point; but as will be seen later, the classical operations never fulfill this requirement, and their failure to do so probably accounts for the numerous and complicated methods devised to overcome faulty drainage. If one examines a cross-section of the chest, one is impressed by the depth of the gutter (costovertebral gutter) which exists on each side of the vertebral column, and by the fact that when the body is recumbent, this gutter constitutes the low point of the pleural cavity. An opening made at the angle of the seventh, eighth or ninth rib will drain the cavity absolutely when the body is recumbent. The low point varies much when the body is in the erect posture because the costodiaphragmatic sulcus is obliterated to a varying degree by adhesions. On the cadaver, Chevrier [4] found

4. Chevrier: Presse méd. **27**:9 (Jan. 9) 1919.

that resection of the sixth rib in the posterior axillary line permitted the retention of 650 c.c. of fluid in the recumbent posture and from 1,250 to 1,300 c.c. in the erect; while resection of the eighth rib in the scapular line caused retention of 300 c.c. in the recumbent posture and from 150 to 200 c.c. in the erect. It is difficult to define precisely the low point for the sitting posture by means of the fluoroscope, and dangerous by means of the aspirating needle. Exploratory operations for the same purpose have occasionally been disastrous, as the operator has penetrated the abdomen through an obliterated pleura and the diaphragm. It is essential that drainage be efficient, whether the patient is lying or sitting. The best plan by which to attain the desired aim is to open the chest by intercostal incision or by costectomy as near as possible to the angle of a convenient rib (seventh, eighth or ninth); and, after slow evacuation of pus, to explore, preferably with the finger, and thus find a point which will be "low" both for the recumbent and erect postures. At this point, guided by the exploring finger or instrument, the chest wall should be incised and tubular drainage established. Through one or both of the openings, it is easy to evacuate the great clots of fibrin so commonly present. Should it be impossible to find a point which will serve efficiently for both postures, the primary opening should be used for a tube, to act when the patient is lying, and the secondary opening should be made with reference to the erect posture alone. When the secondary opening suffices for drainage in both postures, the primary opening may be used for the insertion of Carrel tubes or may simply be covered with dressings. If the general condition of the patient is very poor, it is often wise merely to evacuate the pus through the first incision, and at a later day to complete the operation by exploring and making the second opening for real drainage. The object of the treatment outlined is: first, to keep the patient alive, and second, to establish real, automatic, fool-proof drainage, if possible with one tube, in such a way that it will be effective in any posture the patient is likely to assume.

Many methods have been devised to obtain drainage without permitting air to enter the pleura. Apparently the first of these methods was devised by Bulau,[5] who writes:

> You incise the skin, puncture the chest with a trocar and cannula between a fourth and a fifth inch wide, slip a soft rubber catheter through the cannula, put a clip on it, fix it to the chest wall, connect it by a piece of glass tubing with a long piece of rubber tube filled with lotion, and lower the long tube into some lotion. If you leave a coil of the tube loose on the bed, the patient's movements in bed will not stir the catheter. The objection to my method—that it leaves masses of fibrin in the chest—is unreasonable. I admit that the

5. Bulau: Ztschr. f. klin. Med. **18**:31, 1891, quoted by Paget: Surgery of the Chest, Appendix B.

catheter often gets blocked at first, but either you can put this right by going down the tube with your finger and thumb, or you can syringe limewater up the tube, or in a day or two a fit of coughing will drive a lot of pus into the tube, and set it going again. If the patient keeps feverish, either there is suppuration round the puncture, or the tube is blocked; you had better wait and see what happens, for if you take out the catheter, you can hardly ever get it in again; you ought not to touch it for at least eight days. The catheter does not get nipped by the ribs, for with my method the chest does not fall in. If there is pain, the syphonage must be reduced, unless the pain be due to irritation of the pleura by the catheter. After some time you may let the patient get about, keeping the lower end of the tube in a bottle hung below his chest; later still, you may cut off the tube, and just keep the end of the catheter in place till all is healed. There is no need to wash out the pleura. Even if the pus be offensive, my method will be applicable to the case; but a gangrenous empyema depends on gangrene of the lung, and, therefore, resection is necessary

Bulau's operation was much criticized when promulgated and was given up. In recent years, it has been frequently rediscovered and modified in unessential details. It has also been employed to permit the application of sterilizing solutions to the pleura. It seems to me that Bulau's method, or some uncomplicated modification of it, may be a valuable means by which to tide over a critical period.

STERILIZATION

J. B. Murphy long ago concluded that the only logical plan for the treatment of empyemas, whether of the joints or the pleura, consisted in aspiration and sterilization. After aspiration, he injected a few ounces of 2 per cent. liquor formaldehydi in glycerin. The treatment was repeated, as required, at intervals of a few days, until the effusion became a sterile serosanguineous fluid which was permitted to stay until absorbed. Absorption might take from three to thirty months. His theory was that the liquor formaldehydi kills the microbes and favors polymorpholeukocytosis. The latter means increased numbers of phagocytes with serum containing trypsin resulting from dead polymorpholeukocytes. The trypsin converts albuminoids into peptones which are absorbable. Not much success has followed Murphy's method in the hands of other surgeons.

Frank Hathaway,[6] in cases of pneumococcal empyema, even when staphylococci, but never streptococci, are present, advocates opening the chest sufficiently to admit the hand, permitting removal of pus and all fibrin, separation of adhesions and irrigation with acriflavine until the solution returns clear, then filling the cavity with 2 per cent. iodoform-paraffin and closing with sutures. During the after-treatment, it is necessary to remove with the aspirator each day such iodoform-paraffin as escapes from the chest under the skin. Hathaway remarks that Lord Lister carried out similar treatment twenty-five years before him.

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6. Hathaway, Frank: Brit. M. J. **1**:734 (May 29) 1920.

The methods of Murphy, Lister and Hathaway aim to attain sterilization without drainage. Numerous surgeons have combined methods of sterilization with closed drainage, the drainage being either intermittent or constant and established essentially by Bulau's method. Mozingo [7] by means of a trocar introduces a small rubber tube (4 mm. in diameter) so that from 8 to 15 cm. of the tube (fenestrated) lies within the chest and 15 cm. is outside. Through this small tube, the pus is sucked out by means of a bulb syringe and salt solution, surgical solution of chlorinated soda (Dakin's solution) or liquor formaldehydi in glycerin is introduced. Between treatments, the tube is capped by rubber from a medicine dropper held in place by a serrefine to maintain the negative pressure established by the bulb syringe.[8]

In cases of empyema in which the pneumonia is still active and the temperature is high, Mozingo removes the pus and introduces salt solution every four to six hours for the first few days. Usually the treatments are repeated every two hours by day and every three hours by night. Once daily, the cavity is filled to about half its original capacity with the salt solution; this is to prevent the formation of pockets. As improvement develops, Dakin's solution is substituted for from two to fourteen days, and then once daily. After irrigating with Dakin's solution, a few ounces of 2 per cent. liquor formaldehydi in glycerin are introduced. Usually from three to ten days after beginning the injections of liquor formaldehydi in glycerin, the secretion becomes a sterile serosanguineous fluid, and the tube may be removed. Mozingo writes that he "has never seen a case of empyema too sick to be operated by the closed method and he has operated at least ten cases which were considered nearly moribund when operated." He reports 138 cases of empyema in which treatment by his method was employed with a 2 per cent. mortality rate.

Harloe [9] uses practically the same method as Mozingo, but keeps up constant drainage by means of an electric pump. Whittemore [10] advocates the "air tight" method with the electric pump. He believes in early operation, as "in delayed operation there is more danger of septicemia, pyemia and pericarditis." If after four or five weeks, sterilization is not complete, he resorts to costectomy and packing of the small cavity with gauze. It is easy to combine attempts at chemical sterilization with open drainage; but if the drainage has been properly

7. Mozingo, A. E.: J. Indiana M. A. **13**:46 (Feb.) 1920.

8. J. D. Bryant many years ago used a Politzer bag to establish and keep up negative pressure and receive discharges in ambulant patients.

9. Harloe, R. F.: Treatment of Empyema, J. A. M. A. **73**:1874 (Dec. 20) 1919.

10. Whittemore: Boston M. & S. J. **181**:575 (Nov. 13) 1919.

established and is automatic and "fool-proof," there can be no retention of the sterilizing fluids, and one must have recourse to constant irrigation instead of intermittent instillation and removal of the solutions. When chemical sterilization is desired, Chevrier suggests that it can be more easily and effectively accomplished by means of gases than by liquids. It is easy to pass air, or better, oxygen, through a wash bottle containing ether, liquor formaldehydi or some such volatile material, and conduct it into the pleura through the dependent drainage opening, whence it spreads uniformly through the whole cavity to be sterilized.

In a small proportion of cases in which the simpler methods of drainage have failed, it will be necessary to adopt more extensive and hazardous measures, such as Lilienthal has dubbed "major thoracotomy." By this means, it is possible to survey the diseased regions openly, and, using surgical judgment, to recognize and treat the cause of failure of the simpler procedures. Interlobar or other pockets may be properly opened; lung abscesses treated while sclerosed and contracted membranes covering the visceral pleura may be stripped off (Delorme, Fowler) or incised in criss-cross fashion (Ransohoff). In fact, the ordinary principles of surgery may be carried out, and, if possible, the horrible operations of thoracoplasty avoided.

LUNG EXPANSION

Whatever method or methods are used for the treatment of empyema, it is essential that the lung must be encouraged to expand into its normal position against the chest wall. Blowing exercises are of great value as are also calesthenics or "setting up" exercises properly supervised. The exercises should be such as are interesting to the patient, otherwise they will be dodged as much as possible.

A review of the recent literature on empyema makes it plain that good results may be obtained by various means. There are many roads to Rome. Some travelers like hilly paths, while others prefer the smoother highways. Some surgeons require the stimulus of complicated methods; others prefer less complex, but equally efficient, means. Only the poor and the very rich can afford the constant expert attention required for the successful use of some of the more complicated methods devised for the treatment of empyema. Dodge [11] writes:

> I am now firmly of the opinion that the long established principles of surgery as evolved by many years of experience in civil life and enunciated in practically every textbook on surgery as the proper treatment of empyema have not been shaken from their foundation by any of the fads and fancies evolved during the war period.

11. Dodge, W. T.: Empyema at Base Hospital, Camp Sherman, Ohio, J. A. M. A. **72**:1808 (June 21) 1919.

I feel strongly that in empyema the chest should be opened at the angle of the seventh, eighth, or ninth rib, and after slow evacuation of the pus, the finger should explore the cavity and find that point which will be "low" both for the erect and recumbent postures. At this low point, free drainage should be established. If the drainage is established properly, and at the proper, not necessarily the classical, places, Nature will almost surely provide far better sterilizing agents than can the laboratory of the chemist.

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